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Indian Journal of Chemistry

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Communications

3-Azido-2,3-dideoxy-D-erythropentose: A Precursor for 3′-Azido-3′-deoxythymidine (AZT)†

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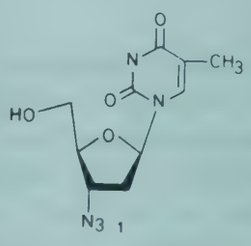
Received 31 *August* 1987; *accepted* 21 *September* 1987

3-Azido-2,3-dideoxy-D-erythropentose, a precursor for AIDS drug AZT, has been synthesised from D-xylose.

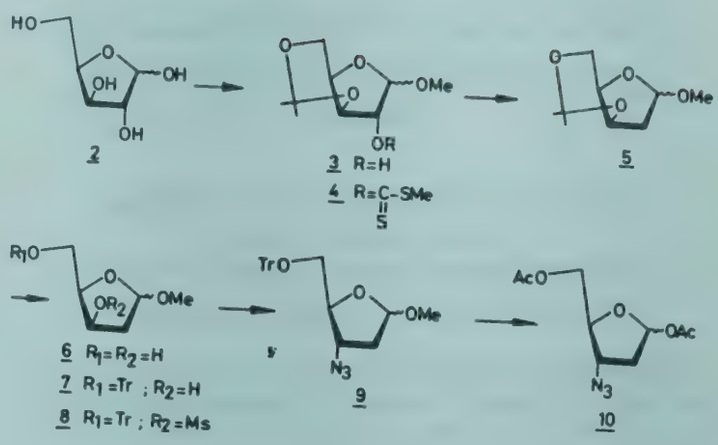
The only drug approved[1] recently for the treatment of AIDS has been 3′-azido-3′-deoxythymidine (**1**) (AZT). Over the years, AZT was prepared[2] for biological studies from thymidine by a classical approach. However, urge to develop inexpensive approach which could also offer a way to make new analogues of AZT for structure-activity relationship, has been renewed in recent years.



The reports by Fleet and Son[3], and Gurjar *et al*[4], as well as earlier report by Dyatkina and Azhayev[5] for the synthesis of 3-azido-2,3-dideoxy-D-erythropentose testify the fact. The publication from Fleet and Son prompted us to disclose new findings of our second approach towards **10** because both the strategies have similar footings.

Methyl 3,5-O-isopropylidene-D-xylose (**3**) obtained[6] from D-xylose (**2**) in two steps, was deoxygenated at position-2 by Barton-McCombie procedure[7]. For instance **3** was successively treated with sodium hydride-carbon disulfide-methyl iodide to afford the xanthate derivative (**4**). Although the PMR spectrum of **4** was complex due to α, β-glycosides, peaks corresponding to S-methyl and H-2 protons were clearly observed.

†RRL-H Communication No. 2089.



Treatment of **4** with freshly prepared tri-*n*-butyltin hydride in refluxing toluene and catalytic amount of α,α′-azo-bis-isobutyronitrile furnished the deoxy product (**5**) in 60% yield.

The presence of a multiplet in the upfield region at δ 2.0 clearly suggested that the transformation has occurred. Removal of the isopropylidene group in the presence of PTSA in methanol gave the diol (**6**) (40%) whose primary hydroxyl was selectively protected as a trityl ether (**7**) (80%). **7** was treated with methanesulfonyl chloride-pyridine mixture to afford the 3-mesylate (**8**), which was heated at 100° with excess of sodium azide in DMF to give the 3-azide (**9**) (70%). The IR spectrum indicated the characteristic absorption at 2100 cm^{-1} for the azido group. Hydrolysis of the trityl group as well as methyl glycoside was effected with aqueous acetic acid at 100° and the corresponding hemiacetal was protected as 1,5-diacetate (**10**) by treatment with acetic anhydride-pyridine. **10** was found to be identical with the sample prepared earlier[4].

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Photochemical D-Ring Expansion in 16α,17α-Methylenepregnenolone Acetate

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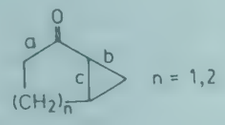
Received 21 *August* 1987; *accepted* 22 *September* 1987

Photochemical conversion of 16α,17α-methylenepregnenolone acetate (**2**) into D-homo-$\Delta^{17,17a}$-pregnenolone acetate (**3**) in 50% yield is described. The reaction provides a new preparative route to D-homosteroids.

Recent investigations on the photochemistry of bicyclo[4.1.0]hepta-2-one (**1**, n = 2) and bicyclo[3.1.0]hexan-2-one (**1**, n = 1) derivatives suggest that the manner of photochemical reorganisation in these systems is quite sensitive to ring size and location of substituents[1-3]. An analsis of product profile in the known reorganisations reveals preference for fission α-bond (a) or β-bond (b) over that of β-bond (c) the propensity of the outer bond (b) to cleave has been attributed[1-4] to ground state overlap between the C=O π-orbital and the bond (b); overlap between the more strained bond (C) and the CO π-orbital is prevented due to their orthogonal disposition.



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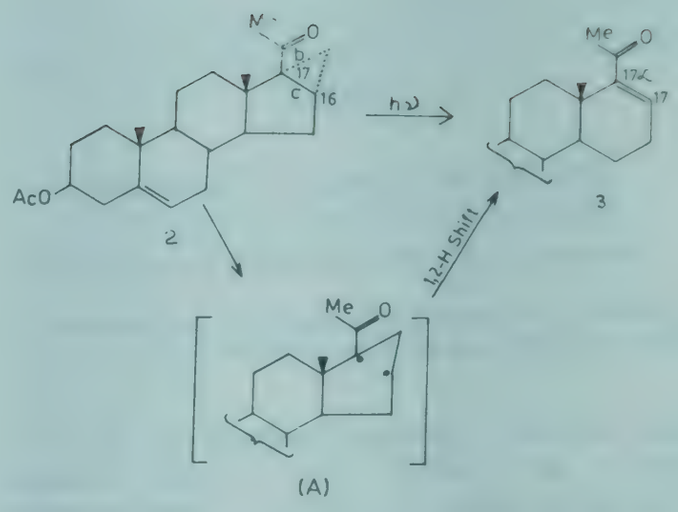
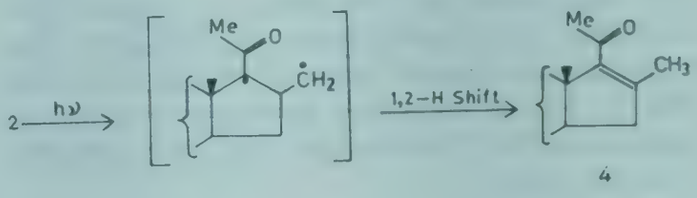
We wish to report that photoreorganisation of 16α,17α-methylenepregneolone acetate **2**, in which the bicyclo-[3.1.0]hexane moiety has the C=O group located outside the ring system, leads to D-homo-$\Delta^{17,17a}$-pregnenolone acetate (**3**) in good yield (~ 50%), apparently involving cleavage of bond (c) in this case (see structure A).

A 0.1% solution of **2**[5] in anhydrous benzene, on irradiation with a 125 watt medium pressure Hg arc for 6 hr and subsequent chromatography (8 silica gel G-coated PLC plates, benzene), furnished **3**, a semi-solid, in 50% yield. The structure of **3** was revealed by its mass spectrum (*m/z* 370, M^+) and a comparison of its IR and PMR spectra with that of **2**. In the transformation 2 → 3,





the intense C_{20}=O absorption in the IR[6] shifted from 1685 to 1665 cm^{-1}, while the PMR spectra recorded disappearance of the characteristic cyclopropane protons in **2** (^{1}HNMR: δ 0.75-0.86, *m*) and appearance of a C=O conjugated olefinic bond in **3** (^{1}HNMR: δ 6.60, *t*, 1H, $C_{17\text{-}H}$, $^3J_{16,17}$ = 3.62 Hz; ^{13}CNMR: δ 160.0 and δ 138.9, C-17α and C-17; other spectral features of **2** and **3** were more or less identical.

We suggest that, *inter alia*, overlap between C=O π bond and the bond (c) made possible in a preferred rotameric ground state conformation of the acetyl group in **2** may have contributed to preferential bond (c) cleavage in this case. A product such as **4**, which would have resulted from bond (b) cleavage in **2** in a photoreaction analoous to that of other known bicyclo[3.1.0]hexane systems[1-3], was not detected in the photolysis mixture.

The photo-rearrangement, **2** → **3** displays potential for a novel preparative route to D-homo-steroidal molecules beginning with $\Delta^{16,17}$-20-keto-steroids.

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5 **2** was prepared from 16-dehydropregnenolone acetate and dimethylsulfoxonium methylid as described in the literature [Steinberg N G, Reasmusson G H and Reamer R A, *J Org Chem*, **44** (1979) 2294], and its structure was checked (^{1}HNMR, ^{13}CNMR, IR, mass).

6 **3**; IR (KBr pellet): 1735 (s), 1665(s), 1625(m-w), 1460(m), 1385(m-s), 1260(s), 1035(m), ·950(m-w), 900(m-w) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.25 (*s*, 6H), 2.03 (*s*, 3H), 2.24 (*s*, 3H), 4.58 (*m*, 1H), 5.37 (*d*, 1H, J=3.42 Hz), 6.60 (*t*, 1H, J=3.60 Hz); ^{13}CNMR ($CDCl_3$): δ 200.4, 170.2, 160.0, 139.7, 138.9, 122.2, 73.8, 49.6, 37.8, 34.4, 31.7, 30.8, 29.7, 28.2, 27.6, 26.8, 21.5, 20.1, 19.4, 19.1 and 18.8; MS: *m/z* 370 (2, M^+), 311 (100).

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Photochemical Addition of Isophorone to Allenic Esters

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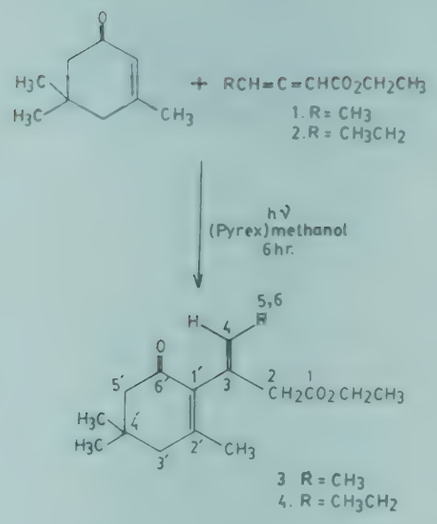
UV irradiation (pyrex filter) of isophorone in presence of ethyl 2,3-pentadienoate (**1**) and ethyl 2,3-hexadienoate (**2**) in methanol yields a single geometric isomer each of the respective addition compounds, **3** and **4**, as the major products.



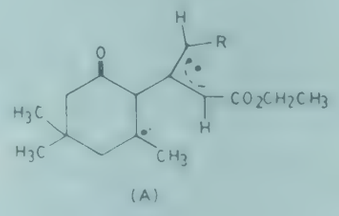
Allene has been reported to photoadd, in a 2+2 manner involving one of its double bonds, to cyclic α,β-unsaturated ketones to produce cyclobutanes in good yield[1-4]. However, aromatically-conjugated ketones and thiones such as benzophenone, thiobenzophenone or xanthenthione, on photolysis (triplet excitation) in the presence of allenes bearing alkyl, alkoxy or aryl substituents at C−1, form oxetanes, thietanes or thiopyrans involving, respectively, 2+2 and 2+4 cycloaddition reactions[5-7]. We wish to report a photoreaction, in methanol, of isophorone with allenic esters i.e., ethyl 2,3-pentadienoate (**1**) and ethyl 2,3-hexadienoate (**2**) which leads to novel addition compounds, **3** and **4** respectively, as the major products.

Isophorone procured from E. Merck was distilled before use, and allenic esters, **1** and **2**, were prepared according to the method reported in the literature[8].

When a mixture of isophorone (3 mmol)[8] and allenic ester (**1**, 11 mmol) in methanol† (350 ml) was irradiated (pyrex filter) with a 125-Watt medium pressure Hg arc for 6 hr and the photolysate chromatographed (silica gel, pet. ether-benzene, 1:1), the adduct (**3**, a colourless viscous oil) was obtained in 18% yield‡. **3** (M^+ at *m/z* 264) revealed the presence of a C=C−C=O moiety (ν_{max} 1665 cm^{-1}) corroborated by its UV spectrum[9], and of an ester function (ν_{max} 1725 cm^{-1}) confirmed by its ^{13}CNMR spectrum[9]. Its full structure was ascertained from its ^{1}HNMR spectrum which revealed the absence of characteristic C_2-H signal at δ 5.88 of isophorone, and the presence of a 1H quartet, in the olefinic region, at δ 5.40 (C_4−H, J=6.69 Hz) and a 2H broad singlet at δ 3.24 (C_2−Hs) along with other resonances due to the pentadienoate part. The existence of only one quartet in the olefinic region (δ 5.40) rules out the presence of isomers involving C_3-C_4 double bond in **3**; the assigned geometry around the C_3-C_4 bond is based on the absence of any observable long range coupling involving C_4-H and C_2-Hs[cf.10].

A photoreaction of isophorone and allenic ester (**2**), when carried out under similar conditions, led to isolation of **4** (a thick oil)[11] in 20% yield as a major product.

The C_3-C_4 double bond geometry obtaining in the adducts (**3** and **4**) is rationalised in terms of involvement of excited triplet isophorone leading to adduct diradical intermediate (A) in which the bulky groups (R, CO_2Et) stay away from the cyclic radicaloid moiety.



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†The chromatogram, on further elution with benzene, furnished minor products (5% yield) characterised as cyclobutane adducts derived from isophorone and allenic ester.

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9 Compound (**3**) gave following spectral data: UV (EtOH): 240 nm; IR (neat): 1725 (s), 1665 (s); ^{1}HNMR ($CDCl_3$): δ 5.40 (*q*, 1H, C_4-H, $J=6.69$ Hz), 4.06 (*q*, 2H, $J=7.08$ Hz, $-CO_2CH_2CH_3$), 3.24 (*bs*, 2H, C_2-Hs), 2.50-1.84 (*m*, C'_3- and C'_5-Hs, $C_{2'}-Me$), 1.78 (*d*, $J=6.69$ Hz, C_5-Hs), 1.21 (*t*, 3H, $-CO_2CH_3$), 1.03 (s, 6H, C'_4-methyls); ^{13}CNMR($CDCl_3$): δ 200.6 (C=O, C-6), 171.6 (C=O, C-1), 155.4 (C-2′), 129.0 (*d* in SFORD, C-4), 128.8, 122.1 (olefinic C-1′, C-3), 60.5 ($-CO_2CH_2CH_3$), 51.3, 46.5, 32.6, 28.9, 27.9, 22.6, 15.2, 13.7; MS: (*m/z*) 264 (5, M^+), 83 (100).

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11 Compound (**4**) gave following spectral data: UV (EtOH): 240 nm; IR (neat): 1725 (s), 1670 (s); ^{1}HNMR ($CDCl_3$): δ 5.31 (*t*, 1H, $J=7.10$ Hz, C_4-H), 4.05 (*q*, 2H, $J=7.08$ Hz, $-CO_2CH_2CH_3$), 3.23 (*bs*, 2H, C_2-Hs), 2.56-1.80 (*m*, C'_3-, C'_5- and C_5-Hs, C_2-Me), 1.22 (*t*, 3H, $-CO_2CH_2CH_3$), 1.16-0.84 (*m*, *t* at 1.20 and *d* at 1.03); ^{13}CNMR ($CDCl_3$): δ 200.1 (C=O, C-6), 171.4 (C=O, C-1), 154.8 (C-2′), 134.0 (*d* in SFORD, C-4), 127.8, 118.0 (olefinic Cs, C-1′, C-3), 60.6 ($-CO_2CH_2CH_3$), 51.2, 46.8, 32.6, 28.5, 27.9, 24.2, 22.9, 13.9, 12.8; MS: (*M/z*) 278 (5, M^+), 83 (80), 71 (100).

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A New Synthesis of Dictamnine, Evolitrine & 6-Methyldictamnine

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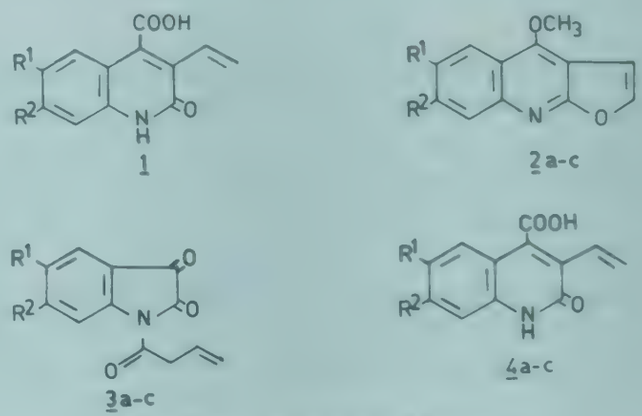
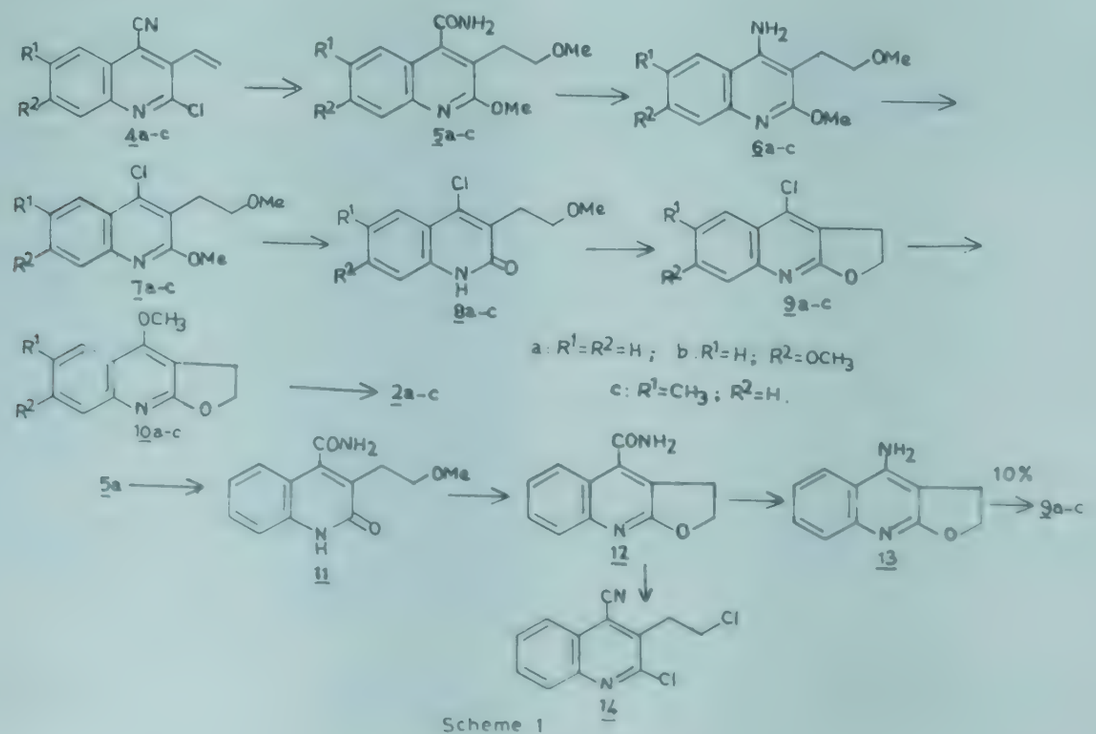
A new synthesis of dictamnine (**2a**), evolitrine (**2b**) and 6-methyldictamnine (**2c**) starting from 4-carboxy-3-vinyl-2-quinolones (**1a-c**) is reported.

The dictamnine group of alkaloids which occur widely in the Rutaceae have been characterised as derivatives of furo[2,3-*b*]quinoline system and derived synthetically from varied types of precursors including 2-quinolones[1]. It was felt that a neat entry into this system could also be gained by way of 2-quinolones, such as **1**, with a vinyl moiety at C-3. The elaboration of **1a-c** into the alkaloids, dictamnine (**2a**), evolitrine (**2b**) and 6-methyldictamine (**2c**), respectively forms the subject of this paper. 4-Carboxy-3-vinyl-2-quinolones (**1a-c**) are easily accessible[2] via N-(3-butenoyl)isatins (**3**).

The quinolinylnitrile (**4a**), obtained from **1a** by treatment of its amide with phosphoryl chloride, on reaction with alkaline H_2O_2 in methanol was transformed into the carboxamide (**5a**). The aminoquinoline (**6a**) obtained from **5a** by Hofmann reaction readily afforded, on diazotisation followed by Sandmeyer reaction, the chloroquinoline (**7a**) which when heated with ethanolic hydrochloric acid furnished **8a** almost quantitatively. Cyclisation of **8a** with polyphosphoric acid gave





Scheme 1

4-chloro-2,3-dihydrofuro[2,3-*b*]quinoline (**9a**)[3,4] which with sodium methoxide in boiling methanol, furnished dihydrodictamnine (**10a**)[3], identical in all respects with an authetic sample prepared according to the method of Cook and Haynes[5]. Dehydrogenation[6] of **10a** with DDQ afforded dictamnine (**1a**) quantitatively (Scheme 1). Extension of this productive sequence to **3b** and **3c** yielded evolitrine (**2b**) and 6-methyldictamnine (**2c**) respectively. The ease of operation and good overall yield render the above technique a valuable addition to the methods hitherto known for the synthesis of dictamnine group of alkaloids.

As an alternative way of arriving at **10a** we heated **6a** with aqueous hydrochloric acid when it gave the quinolone (**11**) quantitatively. On heating with polyphosphoric acid **11** gave a compound, the structure of which was assumed to be **12** on the basis of elemental analyses, IR and mass spectra. PMR spectrum could not be recorded due to poor solubility in common solvents. However, **13** on treatment with phosphoryl chloride gave the nitrile (**14**, the structure of which was confirmed by its PMR spectrum. The amino compound (**13**), derived from **12**, when subjected to a diazotisation-Sandmeyer reaction sequence gave **10a** only in a low yield.

Experimental Procedure

Melting points were determined on a Boetius microheating table and are uncorrected. PMR spectra were recorded ($CDCl_3$) on a Hitachi R600 spectrometer (FT) using TMS as an internal standard and the IR spectra (KBr) on a Perkin-Elmer model 597 spectrophotometer.

The new acid **1b** was prepared from 6-methoxyisatin by a similar procedure[2] adopted for **1a** and **1c**.

2-*Chloro*-4-*cyano*-3-*vinylquinolines* (**4a-c**)

A mixture of **1** (0.02 mol), dry benzene (20 ml) and thionyl chloride (5 ml) was refluxed on a steam-bath for 45 min, concentrated the residue dissolved in dry chloroform and added dropwise to an ice-cold and well-stirred ammonia solution (25% 200 ml) through which ammonia gas was bubbled during the addition. The solid amides from **1a-c** were collected, and recrystallized from aq. ethanol in very good yields (~80-90%, m.p. 300°. These amides were used as such in the next step.

The amide (0.01 mol) was heated with phosphoryl chloride (10 ml) on a steam-bath for 5 hr. After removing the excess phosphoryl chloride *in vacuo*, the residue was digested with ice-water (50 ml) and extracted with benzene (3×20 ml). The solid obtained after evaporation of the solvent was chromatographed over alumina in benzene. The colourless solid obtained after removal of the solvent was recrystallized from benzene-petroleum ether (60-80°) to furnish the cyanoquinolines (**4a-c**) as colourless needles, respectively from the starting **1a-c** (Table 1).

4a:IR:2230 cm^{-1} (CN); PMR:δ 5.87-6.32 (2*dd* 2H, $-CH=CH_2$), 6.81-7.26 (*dd*, 1H, $-CH=CH_2$), 7.55-8.37 (*m*, 4H, ArH).

2-*Methoxy*-3-(2-*methoxyethyl*)*quinoline*-4-*carboxamide* (**5a-c**)

To a solution of sodium hydroxide (2.5g) in methanol (50 ml) was added **4** (0.003 mol) followed by hydrogen peroxide solution (4 ml, 30%). the reaction mixture was kept at 40-60° for 1 hr with occasional shaking and heated at reflux for 4 hr on a steam-bath. It was cooled, mixed with chloroform (100 ml) and shaken well. The chloroform extract was separated, washed with water (3×20 ml), dried and evaporated to give a residue which was recrystallised from pet. ether (60-80°) containing traces of benzene to afford the carboxamids (**5a-c**) (Table 1) from the nitriles (**4a-c**) respectively.

5b:IR:3350, 3175 (NH_2) and 1640 (CO) cm^{-1}; PMR:δ3.10 (*t*,2H, $-CH_2OCH_3$), 3.20 (*s*,3H, $-CH_2OCH_3$), 3.75 (*t*,2H, $-CH_2CH_2OCH_3$), 3.88 (*s*,3H, 7-OCH_3), 4.10 (*s*,3H, C_2-OCH_3), 6.35 (*bs*, 2H,NH_2), 7.50-7.80 (*m*,2H, C_6,C_8-H), 7.90 (*d*, 1H, C_5-H).

4-*Amino*-2-*methoxy*-3(2′-*methoxyethyl*)*quinolines* (**6a-c**)

To an ice cold sodium hypobromite solution [prepared from sodium hydroxide (250 mg) in water (10 ml) and bromine (0.06 ml)] was added **6** (0.001 mol) in one lot and stirred till a clear solution was obtained. It was heated at 70° for 45 min, cold water (10 ml) added and extracted with chloroform (5×25 ml). The extract was dried and evaporated to give a residue which was placed over a column of alumina and eluted with pet. ether (40-60°°) containing traces of benzene. Recrystallization from pet. ether furnished the aminoquinolines (**6a-c**) as colourless crystals from the carboxamids (**5a-c**) respectively (Table 1).

6c:IR(KBr):3475, 3375 cm^{-1} (NH_2); PMR ($CDCl_3$/TMS):2.40 (*s*,3H, 6-CH_3), 2.91 (*t*,2H, -CH_2OCH_3), δ(PPM); 3.26 (*s*,3H, -$CH_2CH_3OCH_3$), 3.60 (*t*,2H, -$CH_2CH_2OCH_3$), 4.05 (*s*,3H, 2-OCH_3), 4.93 (*bs*, 2H, NH_2), 7.28 (d,C_7-H), 7.59 (*d*,C_5-H), 7.77 (*d*,C_8-H).

Table 1—Physical Properties of Various Compounds

Compd†	Yield (%)	m.p. (°C)	Mol formula (M^+)
1	85	210	$C_{13}H_{11}NO_4$ (245)
4a	86	125-26	$C_{12}H_7N_2Cl$ (214)
4b	85	155-57	$C_{13}H_9N_2ClO$ (244)
4c	90	117-18	$C_{13}H_9N_2Cl$ (228)
5a	98.5	139-40	$C_{14}H_{16}N_2O_3$ (260)
5b	98.5	179-80	$C_{15}H_{18}N_2O_4$ (290)
5c	95.5	148-50	$C_{15}H_{18}N_2O_3$ (274)
6a	76	107-8	$C_{13}H_{16}N_2O_2$ (232)
6b	76	77-79	$C_{14}H_{18}N_2O_3$ (282)
6c	74	110-11	$C_{14}H_{18}N_2O_2$ (246)
7a	72	68-69	$C_{13}H_{14}NO_2Cl$ (253)
7b	74	74-75	$C_{14}H_{16}NO_3Cl$ (283)
7c	75	55-56	$C_{14}H_{16}NO_2Cl$ (267)
8a	99	194-95	$C_{12}H_{12}NO_2Cl$ (239)
8b	96	187-88	$C_{13}H_{14}NO_3Cl$ (269)
8c	98	177-78	$C_{13}H_{14}NO_2Cl$ (283)
9a	95	115-16 [lit[3], 115-16]	$C_{11}H_8NOCl$ (207)
9b	94	162	$C_{12}H_{10}NO_2Cl$ (237)
9c	93	150-51	$C_{12}H_{10}NOCl$ (221)
10a	65	103-4 [lit[3,4], 103-4]	$C_{12}H_{11}NO_2$ (201)
10b	68	135-36 [lit[5], 137-37.5]	$C_{13}H_{13}NO_3$ (231)
10c	94	137-38	$C_{13}H_{13}NO_2$ (215)
11	64	235	$C_{13}H_{14}N_2O_3$ (246)
12	88	> 300	$C_{12}H_{10}N_2O_2$ (214)
13	70	> 320	$C_{11}H_{10}N_2O$ (186)
14	65	101-2	$C_{12}H_8N_2Cl_2$ (251)

† All the compounds gave satisfactory C, H analysis.

4-Chloro-2-methoxy-3(2'-methoxyethyl)quinolines (**7a-c**)

The aminoquinoline **6** (2 ml, 0.001 mol) was dissolved in conc. hydrochloric acid (2 ml) containing water (0.5 ml) and cooled to 10°C. An ice cold solution of sodium nitrite (70 mg) in water (2 ml) was added beneath the surface of the solution. After 5 min the cold diazonium chloride solution was added with shaking to a solution of cuprous chloride [prepared from $CuSO_4$ (500 mg)] in conc HCl kept at 5°C. The solution was allowed to stand for 30 min in an ice-bath and then at the room temperature for 1 hr. The reaction mixture was extracted with chloroform (4 × 2 ml), the extract dried and evaporated to give a residue, which was purified by passing through a column of alumina in petroleum ether. The solid obtained after evaporation of the solvent was recrystallized from pet. ether (40-60°) to **7a-c** as colourless crystals from **6a-c** respectively (Table 1).

7a:IR(KBr)cm^{-1}:No NH_2 absorption; PMR ($CDCl_3$/TMS):3.20-3.62 (2*t*, overlapped, 4H, $-CH_2CH_2OCH_3$), δ(PPM):3.39 (*s*,3H, $-CH_2CH_2OCH_3$), 4.11 (*s*,3H, 2-OCH_3), 7.26-8.20 (*m*,3H, C_6 C_7,C_8-H), 8.32 (*d*, V_5-H).

4-Chloro-3-(2'-methoxyethyl)quinolin-2(1H)-ones (**8a-c**)

7 (0.001 mol) was heated with 5% ethanolic hydrochloric acid (7 ml) on a steam-bath for 1 hr. The solution was concentrated to a small bulk and cooled, when **8** separated out as colourless crystals, which was recrystallized from ethanol to give **8a-c** from the corresponding **7a-c** (Table 1).

4-Chloro-2,3-dihydrofuro[2,3-b]quinolines (**9a-c**)

A mixture of **8** (0.001 mol) and polyphosphoric acid (5 ml) was heated at 120° for 2.5 hr. After cooling, crushed ice was added and the solution was basified with ammonia and extracted with chloroform (4 × 25 ml). The extract was dried and evaporated to give a residue which was chromatographed over alumina in benzene. Recrystallization from benzene-pet. ether furnished **9** as colourless crystals (Table 1).

9c:IR(KBr):1620, 1560 cm^{-1} (C=C); PMR ($CDCl_3$/TMS):2.46 (*s*,3H, 6-CH_3); δ(PPM):3.28 (*t*,2H, OCH_2CH_2), 4.68 (*t*,2H, OCH_2-); 7.34-7.85 (*m*,3H, ArH).

4-Methoxy-2,3-dihydrofuro[2,3-b]quinolines (**10a-c**)

9 was reacted with sodium methoxide in methanol and the product worked-up to furnish **10**, according to the method reported earlier for **10a**[3].

10a:IR(KBr):1620, 1575 cm^{-1}; PMR ($CDCl_3$/TMS):3.56 (*t*,2H, $-OCH_2CH_2$), 4.15(*s*,3H, $-OCH_3$), δ(PPM):4.58 (*t*,2H, $-OCH_2CH_2$), 7.15-7.90 (*m*,3H,$C_{6'}$,$C_{7'}$,C_8-H, 8.16 (*d*,1H,C_5-H).

4-*Methoxyfuro*[2,3-*b*]*quinolines* (**2a-c**)

Dehydrogenation of **10a-c** by DDQ in dioxan according to the method Piozzi *et al.*[6] afforded **2a-c** (Table 1).

3-(2′-*Methoxyethyl*)*quinolin*-2(1*H*)-*one*-4-*carboxamide* (**11**)

7a (0.001 mol) was mixed with 5% aq. hydrochloric acid (7 ml), heated on a steam-bath for 45 min, cooled, diluted with water, and neutralised with dil ammonia. The solid that separated was collected and crystallized from methanol as colourless crystals (Table 1).

2,3-*Dihydrofuro*[2,3-*b*]*quinoline*-4-*carboxamide* (**12**)

11 (0.001 mol) was mixed with polyphosphoric acid (6 ml) and heated at 120° till the mixture became homogeneous. It was cooled, poured into ice water and filtered. The clear filtrate was basified with ammonia and solid that separated was collected and crystallized from aq, ethanol as colourless crystals (Table 1).

Reaction of **12** *with phosphoryl chloride*

12 (0.001 mol) was heated with phosphoryl chloride (5 ml) at 110° for 3 hr. cooled and poured into ice water. It was basified with ammonia and extracted with chloroform. The chloroform extract was dried and evaporated to give a residue which was purified by column chromatography over alumina. Elution with pet. ether (60-80°) gave 2-chloro-3(2′-chloroethyl-4-cyanoquinoline (**14**) as colourless crystals (Table 1). It was found to be identical with the product derived from 2-chloro-3(2′-hydroxyethyl)quinoline-4-carboxamide[2], by a similar treatment.

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Synthesis of (±)-Pterosin-M & Onitin†

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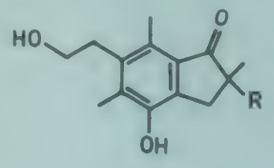
2,4-Dimethyl-3-carbomethoxymethylanisole (**3**) on LAH reduction gives the alcohol (**4**) which is converted into the methyl ether (**5**). Formylation of **5** to **6**, followed by Horner reaction on **6** with the appropriate phosphonate yields the unsaturated ester (**7**) which is converted by hydrolysis and hydrogenation into the dihydrocinnamic acid (**9**). Cyclodehydration of **9** with HF leads to the indanone dimethyl ether (**10**) which on demethylation with HBr/gl AcOH affords (±)-pterosin-M (**1**). Conversion of **10** into the ketodimethyl dimethyl ether (**11**), followed by ether cleavage with HBr/gl AcOH gives onitin (**2**).

In continuation of our studies on the synthesis of pterosins[1], we report herein the synthesis of pterosin-M[2] (**1**) and onitin[3,4] (**2**), starting from the known tetrasubstituted benzene[1c] (**3**).

LAH reduction of **3** led to the alcohol (**4**) which was converted into the methyl ether (**5**) using NaH and CH_3I in dioxan, following the procedure of McMorris *et al.*[5] Formylation[6] of **5** to **6** followed by Horner reaction[7] on **6** with methyl 2-(diethylphosphono)propionate gave the unsaturated ester (**7**) in high yield. Its *E/Z* ratio was not determined, as the double bond was to be reduced eventually. Metal-ammonia reduction[8] of the acid (**8**) corresponding to **7** furnished the dihydrocinnamic acid (**9**), which on cyclodehydration[9] with HF gave the indanone dimethyl ether (**10**). Its demethylation with HBr in AcOH[5] (80°, 2.5 hr) afforded (±)-pterosin-M (**1**) with its elemental analyses and spectral data tallying with those of the natural product. Demethylation of **10** (HBr-AcOH) at higher temperature (100°) and slightly longer time (3 hr) gave on the other hand 6-β-bromoethyl-4-hydroxy-2,5,7-trimethylindan-1-one (**12**) as an oil, characterized by elemental analyses and PMR data.

Methylation (NaH-CH_3I/THF) of **10** to the ketodimethyl dimethyl ether (**11**), followed by ether cleavage, analogous to **10** giving **1**, completed the synthesis of onitin (**2**), the spectral and elemental data of which agreed with those of the natural product.



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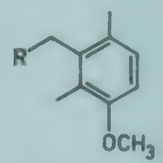

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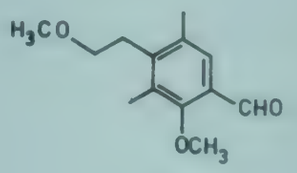

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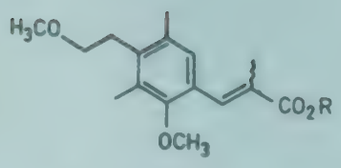

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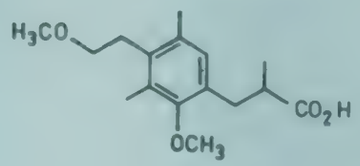

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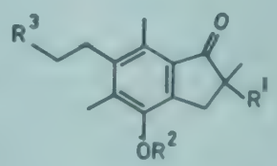

10, R^1 = H; R^2 = CH_3; R^3 = OCH_3
11, R^1 = R^2 = CH_3; R^3 = OCH_3
12, R^1 = R^2 = H; R^3 = Br
1, R^1 = R^2 = H; R^3 = OH
2, R^1 = CH_3; R^2 = H; R^3 = OH

†Part LXXXI in the series, Studies in Terpenoids, Part LXXX, Kesavulu Reddy N & Krishna Rao G S, *Indian J Chem*, **26B** (1987) 920.

Experimental Procedure

Details of instrumentation used, spectral and other data presentation and the extractive work-up of reactions are as mentioned in reference 1c.

2,4-*Dimethyl*-3-*β*-*hydroxyethylanisole* (**4**)

To a stirred suspension of LAH (0.76g, 20 mmol) in dry ether (100 ml) was added **3**[1c] (6.24g, 30 mmol) in ether (50 ml) slowly with stirring. The stirring was continued for 12 hr at room temperature and for 4-5 hr under reflux. Decomposition of excess LAH followed by usual extractive work-up gave **4** (5g, 92%); m.p. 75° (from pet. ether-benzene); PMR ($CDCl_3$); 2.2 (*s*, 3H, Ar-CH_3), 2.26 (*s*, 3H, Ar-CH_3), 3.26 (*t*, J=8 Hz, 2H, Ar-CH_2), 3.76 (*s*, and *t*, merged, 5H, OCH_3 and CH_2OH), 6.6 (*d*, J=8 Hz, 1H, Ar-H_6) and 6.93 (*d*, J=8 Hz, Ar-H_5) (Found: C, 73.4; H, 8.5. $C_{11}H_{16}O_2$ requires C, 73.3; H, 9.0%).

2,4-*Dimethyl*-3-*β*-*methoxyethylanisole* (**5**)

To a slurry of NaH (0.96g, 40 mmol, freed from mineral oil) in dry THF (50 ml), **4** (7.2g, 40 mmol) in THF (10 ml) was added and the mixture stirred for 0.5 hr. To this CH_3I (8.5g) in THF (10 ml) was added slowly and the stirring continued at room temperature for 1 hr. Most of the solvent was distilled off and to the residue water (100 ml) added. Extractive work-up gave **5** (7g, 90%) which on preparative TLC (silica gel, pet. ether) furnished an analytical sample; b.t. 135°/3 mm (Found: C, 74.4; H, 9.2. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.3%).

3,5-*Dimethyl*-2-*methoxy*-4-*β*-*methoxyethylbenzaldehyde* (**6**)

Formylation[1c] of **5** (3.84g, 20 mmol), gave **6** (3.2g, 71%); m.p. 62° (from pet. ether); IR (nujol): 1690 (C=O), 1600 (aromatic); PMR ($CDCl_3$): 2.33 (*s*, 3H, Ar-CH_3), 2.36 (*s*, 3H, Ar-CH_3), 3.03 (*t*, J=8 Hz, 2H, Ar-CH_2), 3.36 (*s*, 3H, OCH_3), 3.66 (*t*, J=8 Hz, 2H, CH_2OCH_3), 3.86 (*s*, 3H, OCH_3), 7.55 (*s*, 1H, Ar-H) and 10.2 (*s*, 1H, CHO) (Found: C, 70.3; H, 8.1. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%).

Methyl 2-*methoxy*-4-*β*-methoxyethyl-2′,3,5-*trimethylcinnamate* (**7**) *and the corresponding acid* (**8**).

Horner reaction[1c] on **6** (2.7g, 12 mmol) gave **7** as an oil (3g, 85%). An analytical sample was obtained by preparative TLC; IR (film): 1710 (C=O), 1640 (C=C), 1600 (aromatic); PMR ($CDCl_3$): 1.96 (*d*, J=2 Hz, 3H, vinylic-CH_3), 2.26 (*s*, 3H, Ar-CH_3), 2.30 (*s*, 3H, Ar-CH_3), 2.86 (*t*, J=8 Hz, Ar-CH_2), 3.2 (*s* and *m*, merged, 5H, OCH_3 and CH_2OCH_3) 3.6 (*s*, 3H, OCH_3), 3.76 (*s*, 3H, OCH_3), 6.8 (*s*, 1H, Ar-H) and 7.6 (*bs*, 1H, C=CH−) (Found: C, 69.9; H, 8.1. $C_{17}H_{24}O_4$ requires C, 69.8; H, 8.3%).

Hydrolysis[1c] of **7** (2.6g, 9 mmol) gave **8** (2.2g, 87%), m.p. 140° (Found: C, 69.1; H, 8.1. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0%).

2-*Methoxy*-4-*β*-*methoxyethyl*-2′,3,5-*trimethyldihydrocinnamic acid* (**9**)

Metal-ammonia reduction[1c] of **8** (1.66g, 6 mmol) gave **9** (1.3 g, 77%); m.p. 79-80° (from pet. ether); PMR ($CDCl_3$): 1.1 (*d*, J=8 Hz, 3H, $CHCH_3$), 2.23 (*s*, 6H, 2×Ar−CH_3), 2.6-3.0 (*m*, 5H, 2×Ar—CH_2 and $CHCH_3$), 3.26 (*s* and *t*, merged, 5H, OCH_3 and CH_2OCH_3), 3.6 (*s*, 3H, OCH_3), 6.6 (*s*, 1H, Ar-H) and 11.2 (*s*, 1H, CO_2H, exchangeable with D_2O) (Found: C, 68.6; H, 8.5. $C_{16}H_{24}O_4$ requires C, 68.5; H, 8.6%).

4-*Methoxy*-6-*β*-*methoxyethyl*-2,5,7-*trimethylindan*-1-*one* (**10**)

Cyclodehydration[1c] of **9** gave **10** (0.8g, 84%); m.p. 76-77° (from pet. ether); IR (nujol): 1700 (C=O), 1590 (aromatic); PMR ($CDCl_3$): 1.28 (*d*, J=8 Hz, $CHCH_3$), 2.36 (*s*, 3H, C_5-CH_3), 2.64 (*s* and *m*, merged 4H, C_7-CH_3 and $CHCH_3$), 3.02 (*t*, J=8 Hz, 2H, Ar-CH_2), 3.36 (*s*, and *t* merged, 5H, OCH_3 and CH_2OCH_3) and 3.80 (*s*, 3H, OCH_3) (Found: C, 73.5; H, 8.5. $C_{16}H_{22}O_3$ requires C, 73.3; H, 8.5%).

4-*Hydroxy*-6-*β*-*hydroxyethyl*-2,5,7-*trimethylindan*-1-*one* [(±)-*Pterosin-M*] (**1**)

Demethylation[1c] of **10** (0.2g, 0.9 mmol) gave (±)-**1** (0.1g, 53%); m.p. 165° (from benzene-pet. ether) (lit.[2] m.p. 187°for the optically active natural product); IR (nujol): 3100-3500 (OH)1600, 1590 (aromatic); PMR (CD_3COCD_3): 1.20 (*d*, J=8 Hz, 3H, $CHCH_3$), 2.32 (*s*, 3H, C_5-CH_3), 2.57 (*s* and *m*, merged, 4H, C_7-CH_3 and $CHCH_3$), 2.98 (*t*, J=8 Hz, 2H, ArCH_2CH_2), 3.27 (*m*, 2H, ArCH_2CHCH_3) and 3.61 (*t*, J=8 Hz, 2H, CH_2OH) (Found: C, 71.3; H, 7.6. Calc. for $C_{14}H_{18}O_3$: C, 71.8; H, 7.7%).

4-*Methoxy*-6-*β*-*methoxyethyl*-2,2,5,7-*tetramethylindan*-1-*one* (**11**)

To a stirred suspension of NaH (24 mg, 1 mmol, freed from mineral oil) in dry THF (5 ml) was added **10** (0.2g, 0.8 mmol) and the reaction mixture stirred for 10 min. To this CH_3I (0.2 ml) was added and the stirring continued for 1 hr. Extractive work-up after pouring the reaction mixture into water (25 ml) gave a viscous liquid which was further purified by preparative TLC to give **11** (0.2g, 90%); IR (film): 1700 (C=O), 1590 (aromatic); PMR (CCl_4): 1.14 (*s*, 6H, CH_3CCH_3), 2.3 (*s*, 3H, C_5-CH_3), 2.58 (*s*, 3H, C_7-CH_3), 2.84 (*s*, 2H, Ar−CH_2), 2.94 (*t*, J=8 Hz, 2H, Ar−CH_2), 3.28 (*s* and *t*, merged, OCH_3 & CH_2OCH_3) and 3.74 (*s*, 3H, OCH_3) (Found: C, 73.9; H, 8.7. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.8%).

4-Hydroxy-6-β-hydroxyethyl-2, 2, 5, 7-tetramethyl-indan-1-one (onitin) (**2**)

A solution of **11** (0.1g, 0.6 mol) in gl. AcOH (6 ml) and HBr (48%, 6 ml) was heated at 80° for 2 hr. The solution was concentrated *in vacuo*. Extractive work-up of the residue, followed by preparative TLC (pet. ether-ethyl acetate, 1 : 2) gave **2** (90 mg, 60%); m.p. 210° (from aq. methanol) (lit.[5] m.p. 214°); MS; 248 (M^+); IR (nujol): 3000-3500 (OH, *b*), 1690 (C=O), 1600, 1590 (aromatic); PMR (CD_3COCD_3): 1.13 (*s*, 6H, CH_3CCH_3), 2.32 (*s*, 3H, C_5-CH_3); 2.57 (*s*, 3H, C_7-CH_3), 2.84 (*s*, 2H, 2×OH, exchangeable with D_2O), 2.86 (*s*, 2H, Ar-CH_2), 2.96 (*t*, J=8 Hz, 2H, ArCH_2CH_2OH) and 3.61 (*t*, J=8 Hz, 2H, CH_2OH) (Found: C, 72.4; H, 8.0. Calc. for $C_{15}H_{20}O_3$: C, 72.5; H, 8.1%).

Acknowledgement

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Organomercury Mediated Synthesis of Isocoumarins

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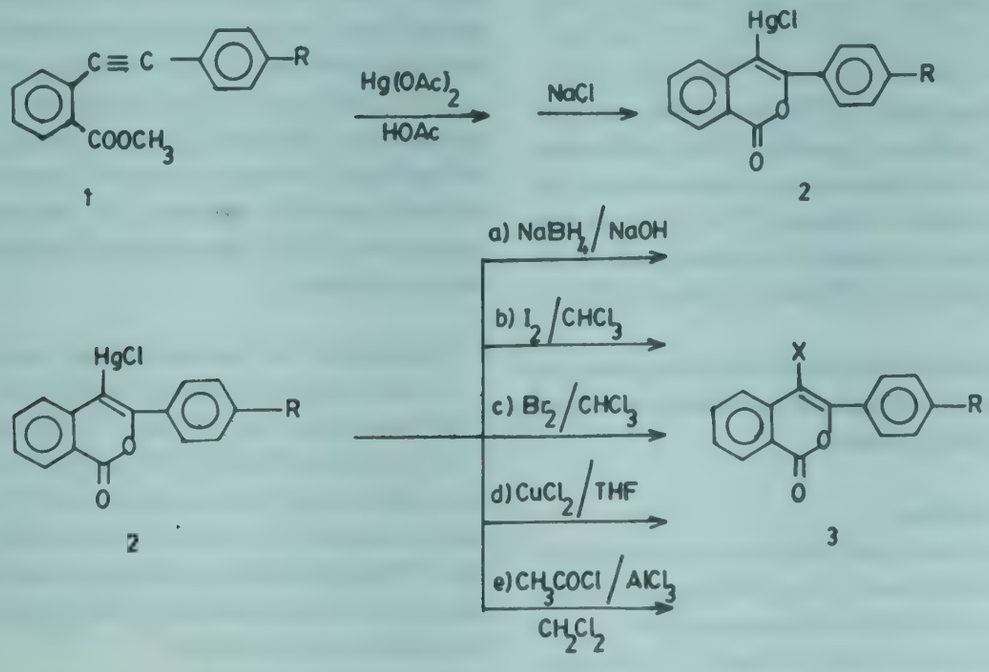
A facile and convenient synthesis of isocoumarins via an organomercurial route is reported. The synthesis involves reaction of methyl 2-alkynylbenzoates with mercuric acetate to give the corresponding isocoumarin mercurials which serve as intermediates to afford the appropriate isocoumarins having substituents as Cl, I, Br, $COCH_3$ etc.

Synthesis of heterocycles via solvomercuration and demercuration has been an exceedingly valuable procedure in organic synthesis. Analogous reactions on acetylenic substrates have proven much less useful apparently due to the tendency of acetylenes to undergo polymercuration[1-3]. However a recent report highlighted the synthesis of heterocycles via intramolecular solvo-mercuration of acetylenic substrates[4]. We now wish to report the intramolecular solvomercuration of methyl 2-alkynylbenzoates to provide isocumarin and its derivatives.

A number of methods are available for the synthesis of isocoumarins[5-9], but these suffer from some limitations such as difficulties in the preparation of starting material and severe conditions for cyclisation. The method now developed involves reaction of methyl 2-alkylbenzoates with mercuric acetate to give the corresponding isocoumarin mercurial and direct replacement of the mercury moiety by various functional groups giving rise to substituted isocoumarins (Scheme 1).

Larock *et al.*[10] reported the synthesis of $\Delta^{\alpha,\beta}$-butenolides by carbonylation of vinyl mercurials obtained from propargylic alcohols and mercuric chloride. However, when this methodology was extended to 2-ethynylphenols, it led to the formation of 2-substituted benzofurans and not to isocoumarins[11]. Hegedus *et al*[12] synthesised isocoumarins from 2-allylbenzoic acid by palladation. Hence it was presumed that palladation of 2-alkynylbenzoic acids could lead to isocoumarins[13]. However, the reaction of 2-carboxydiphenylacetylene with Li_2PdCl_4 or $PdCl_2.2CH_3CN$ in dry THF using Na_2CO_3 as a base did not proceed as expected. Also the change of base did not yield any fruitful result. Hence the solvo mercuration was adopted to get the desired product.



X = a = H ; b = I ; c = Br ; d = Cl ; e = $COCH_3$

R = H ; Cl ; CH_3 ; Br.

SCHEME 1

Table 1—Details of Isocoumarins and Isocoumarin Mercurials Prepared

Sl. No.	Isocoumarin prepared	Yield (%)	m.p. (°C) (lit)	Found (Calc.) (%) C	H
1	3-Phenyl-(**3a**)	62	88-89(89-91)[16]	81.2(81.1)	4.4(4.5)
2	4-Iodo-3-phenyl-(**3b**)	85	136	51.9(51.7)	2.7(2.6)
3	4-Bromo-3-phenyl-(**3c**)	70	131(132)[16]	59.9(59.8)	2.9(3.0)
4	4-Chloro-3-phenyl-(**3d**)	68	117	70.3(70.2)	3.6(3.5)
5	4-Acetyl-3-phenyl-(**3e**)	78	72-73	77.0(77.3)	4.7(4.6)
6	3-(*p*-Chlorophenyl)-(**4a**)	60	141(142)[16]	70.1(70.2)	3.5(3.5)
7	4-Iodo-3-(*p*-chlorophenyl)-(**4b**)	76	180-81	47.3(47.1)	2.1(2.1)
8	4-Bromo-3-(*p*-chlorophenyl)-(**4c**)	75	186	53.6(53.7)	2.5(2.4)
9	4-Chloro-3-(*p*-chlorophenyl)-(**4d**)	72	170	61.7(61.9)	2.8(2.8)
10	4-Acetyl-3-(*p*-chlorophenyl)-(**4e**)	70	110-11	67.9(68.3)	3.6(3.7)
11	3-(*p*-Methylphenyl)-(**5a**)	60	116(116)[15]	81.2(81.4)	5.2(5.1)
12	4-Iodo-3-(*p*-methylphenyl)-(**5b**)	85	174-75	53.2(53.0)	3.1(3.1)
13	4-Bromo-3-(*p*-methylphenyl)-(**5c**)	80	172	60.9(61.0)	3.6(3.5)
14	4-Chloro-3-(*p*-methylphenyl)-(**5d**)	70	128-30	71.1(71.0)	4.1(4.1)
15	3-(*p*-Bromophenyl)-(**6a**)	70	147-48	59.9(59.8)	3.1(3.0)
16	4-Iodo-3-(*p*-bromophenyl)-(**6b**)	82	168-69	42.26(42.15)	2.0(1.9)
17	4-Bromo-3-(*p*-bromophenyl)-(**6c**)	78	204-5	47.48(47.36)	2.1(2.1)
18	4-Chloro-3-(*p*-bromophenyl)-(**6d**)	64	185	53.51(53.65)	2.3(2.4)
19	4-Acetyl-3-(*p*-bromophenyl)-(**6e**)	73	108-9	59.64(59.48)	3.4(3.2)
20	4-Chloromercuri-3-phenyl-	68	208-10	39.7(39.4)	2.1(2.0)
21	4-Chloromercuri-3-(*p*-chlorophenyl)-	63	230-32	36.9(36.6)	1.4(1.6)
22	4-Chloromercuri-3-(*p*-methylphenyl)-	65	225-27	40.5(40.8)	2.6(2.3)
23	4-Chloromercuri-3-(*p*-bromophenyl)-	63	251-52	33.7(33.6)	1.6(1.5)

The starting esters were prepared by the procedure of Castro and Stephens[14] by coupling methyl 2-iodobenzoate with appropriate cuprousphenyl-acetylide in dry pyridine under nitrogen. Mercuration was carried out to obtain isocoumarin mercurial in 60-70% yield by adding the ester to a suspension of mercuric acetate in acetic acid and stirring the mixture at room temperature for 1 hr. The mercury moiety served as an intermediate to get isocoumarins with substituent as H, I, Br, Cl and $COCH_3$. The isocoumarins prepared are listed in Table 1. They were characterised by their spectral (UV, IR and PMR) and analytical data. The infrared spectra (KBr) indicated that the carbonyl absorptions were characteristic of 6-membered unsaturated lactones. The UV spectral data of all the lactones revealed the same pattern of absorptions at around 330, 295 and 250 nm in $CHCl_3$ solution.

The ability to further functionalise intermediate organomercurial greatly expands the synthetic utility of this new heterocyclic approach.

Experimental procedure

The solvents used were purified by standard methods and distilled before use. The melting points reported are uncorrected. Infrared spectra (KBr: ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer 298 IR spectrophotometer, UV spectra in $CHCl_3$ on a Hitachi 220A UV-visible spectrophotometer and PMR spectra ($CDCl_3$) on a Varian EM-390 90 MHz instrument chemical shifts are expressed in δ (PPM) downfield from TMS internal reference. Unless otherwise stated the organic extracts were dried over anhydrous sodium sulphate.

Preparation of organomercurial

To a suspension of mercuric acetate (0.002 mol) in acetic acid (6 ml) was added the ester (I, 0.002 mol). The mixture was stirred at room temperature for 1 hr, poured into saturated sodium chloride-ice mixture and allowed to warm to room temperature, the separated organomercurial was filtered, washed well with hexane and dissolved in chloroform. The chloroform solution was filtered through silica gel, crude mercurial isolated by evaporation of the solvent and recrystallised from 90% ethanol. All the isocoumarin mercurials were fully characterised by their spectral and analytical data.

3-*Substituted isocoumarins* (**3a, 4a, 5a** *and* **6a**)

To the organomercurial (0.001 mol) was added 1:1 THF-water mixture (8 ml). To this solution NaOH (3*M*, 4 ml) and $NaBH_4$ (0.5*M*) in NaOH (3*M*, 8 ml) were added and the mixture stirred 1 hr. Sodium chloride was added to saturate the water layer, mixture filtered through silica gel, extracted with ether, the ethereal extract dried and the solvent evaporated to get the desired isocoumarin.

4-*Iodo*-3-*substituted-isocoumarins* (**3b, 4b, 5b** *and* **6b**)

To organomercurial (0.001 mol) in chloroform (5 ml) was added iodine (0.001 mol) in chloroform (5 ml)

and the mixture stirred for 5 hr. It was filtered through silica gel, washed with aq. potassium iodide (10%), water, dried, solvent evaporated and the residue subjected to column chromatography using benzene as the eluent to furnish the iodocompound.

4-Bromo-3-substituted-isocoumarins (**3c, 4c, 5c** *and* **6c**)

To the organomercurial (0.001 mol) in chloroform (5 ml) was added bromine (0.001 mol) in chloroform (5 ml) and the mixture stirred for 4 hr. It was filtered through silica gel, washed with sodium thiosulphate (10%), water, dried, solvent removed and the residue subjected to column chromatography to furnish the desired bromo compound.

4-Chloro-3-substituted-isocoumarins (**3d, 4d, 5d** *and* **6d**)

To the organomercurial (0.001 mol) in THF (10 ml) was added cupric chloride (0.002 mol) and the mixture refluxed gently for 3 hr. It was filtered, diluted with water (20 ml), extracted with ether, washed well with water, dried, solvent removed and the residue subjected to column chromatograhy using benzene as the eluent to furnish the desired chloro compound.

4-Acetyl-3-substituted-isocoumarins (**3e, 4e** *and* **5e**)

To a mixture of anhydrous aluminium chloride (0.001 mol) and acetyl chloride (0.001 mol) in dry dichloromethane (10 ml) was added the organomercurial (0.001 mol). The mixture was stirred at room temperature for 2 hr, poured into water (30 ml) and extracted with dichloromethane. The combined organic extract was washed with water (20 ml), the aqueous layer combined and reextracted with dichloromethane (2 × 30 ml). The combined organic extract was dried, solvent evaporated and the residue subjected to column chromatography using benzene as the eluent to furnish the desired acetyl compound.

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Synthesis of 4-Isopropyl-1,6-dimethyl-5,8-naphthoquinone (Cadalenequinone)†

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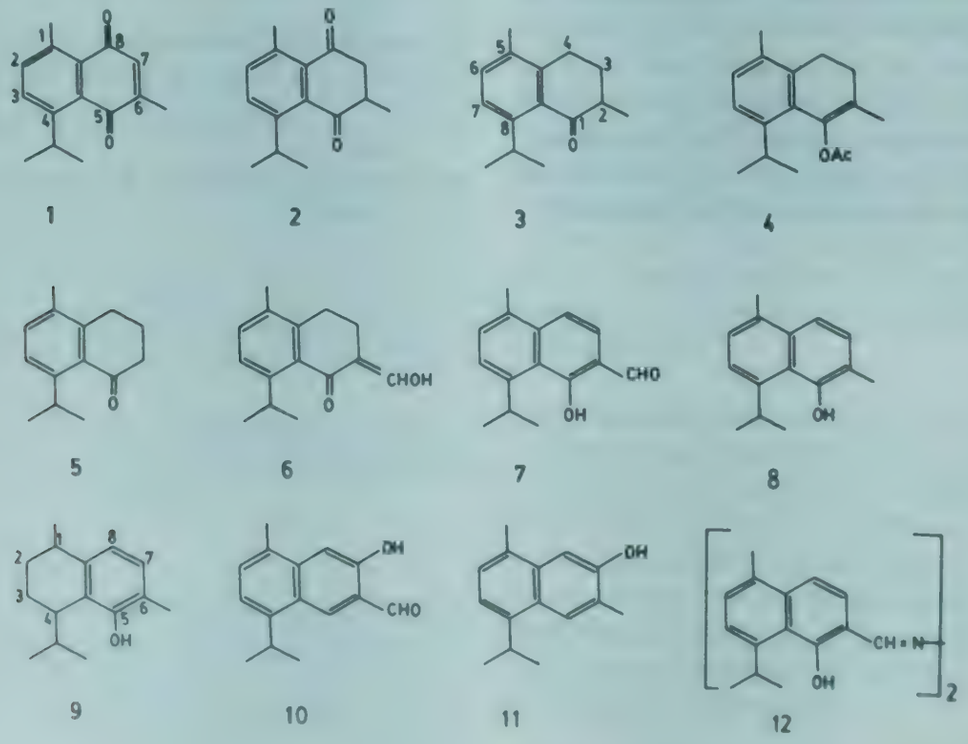
The synthesis of cadalenequinone (**1**), a naturally occurring cadalenic sesquiterpene naphthoquinone is described by two routes, starting from the tetralones **3** and **5** respectively. The first troute from **3** gives **1** in an overall poor yield. The second route from **5** affords **1** in good yield, and also, in addition, two biogenetically interesting hydroxycadalenes (**7**) and (**8**).

From the volatile seed oil of *Stahlianthus campanulatus*, used in Viet-Nam as an antihaemorrhagic drug, two sesquiterpene quinones called cadalenequinone and dihydrocadalenequinone were isolated and their structures established, respectively as **1** and **2** on the basis of spectral properties and chemical correlations[1]. The present paper describes the synthesis of **1** by two routes, one of these affording two additional biogenetically interesting oxygenated cadalenic sesquiterpenes.

The first route for the synthesis of **1** employs a two-reaction sequence, **3**→**4**→**1**, on the known tetralone[2] (**3**), essentially adopting the procedure of McCormick *et al*[3]. While in the original procedure of McCormick *et al.*, enol acetates of tetralones after isolation were treated with DDQ to afford the corresponding naphthyl acetates, in our hands the action of DDQ on the inseparable mixture of **3** and its enol acetate **(4)** led to the formation of cadalenequinone (**1**) in 20% yield, and an unacceptably large recovery (~78%) of **3**. In a separate experiment it was shown that **3** by itself, did not give **1** with DDQ under these conditions.

In view of the poor yield of **1** by this route, an alternate route for its synthesis was explored. The second route, also starting from a known tetra-



† Part LXXX in the series, Studies in Terpenoids. Part LXXIX, Raju B & Krishna Rao G S, *Indian J Chem*, **26B** (1987) 712

lone[2] (**5**), though longer **5**→**6**→**7**→**8**→**1** afforded via its formyl derivative (**6**) two biogenetically significant intermediates, the 5-hydroxycadalenal (**7**) and the 5-hydroxycadalene (**8**) which are related to 5-hydroxycalamenene (**9**) occurring in the *Bazzania* species[4] and the closely analogous 7-hydroxycadalenal (**10**) and 7-hydroxycadalene (**11**) occurring in elm woods[5]; all of them (**9, 10,** and **11**) have earlier been synthesized in our laboratory[6].

Formylation of **5** according to the procedure of Minato and Horibe[7] gave the hydroxymethylene ketone (**6**) which on dehydrogenation with DDQ furnished 5-hydroxycadalenal (**7**). Attempted Wolff-Kishner reduction of **7** gave the unwanted bisazo compound (**12**). However, its reduction with sodium borohydride in refluxing ethanolic sodium hydroxide, according to the procedure introduced by Bell[8] for the reduction of phenolic ketones gave **8** as a labile compound. Its attempted purification either by distillation, or by repeated TLC resulted in oxidation, leading to a mixture of **8** and **1** in various proportions. However, a short (5 min) oxidation by iodoxybenzene[9] of a sample of freshly prepared and spectroscopically characterized **8** gave, in excellent yield (87%), the cadalenequinone (**1**) (58% overall yield from **5**) identical with the material obtained by the first route (**3**→**4**→**1**).

The French workers[1] prepared cadalenequinone (**1**) in 33% yield by chromic acid oxidation of cadalene and reduced it to **2** by zinc and acetic acid. The present independent synthesis of **1** constitutes therefore a formal synthesis of **2** as well.

Experimental Procedure

Melting points (uncorrected) were determined using a Kofler hot stage apparatus. The instruments used for recording UV, IR and PMR spectra were Shimadzu UV-190 double beam spectrophotometer (λ_{max} in nm), Perkin-Elmer 781 spectrophotometer (ν_{max} in cm^{-1}) and Varian T-60 or Jeol FX-900 spectrometer (TMS as internal standard and chemical shifts in δ ppm) respectively. Petroleum ether refers to the petrol fraction, b.p. 60-80°. By extractive work-up is meant the standard sequence: exhaustive solvent extraction of the product/s of a reaction, appropriate washing of the combined organic phase, drying (anhyd. Na_2SO_4) and removal of the solvent.

4-*Isopropyl*-1,6-*dimethyl*-5,8-*naphthoquinone* (*Cadalenequinone*) (**1**)

To a mixture of **3**[2] (0.216 g, 1 mmol) and acetic anhydride (0.5 ml) in CCl_4 (10 ml) was added $HClO_4$ (70%, 0.5 ml). The reaction mixture was stirred at room temperature for 3 hr. The dark red solution was poured into a mixture of pet. ether and saturated aq. $NaHCO_3$ (1:1, 50 ml). Solid $NaHCO_3$ (2 g) was added till the aqueous layer remained slightly basic. The aqueous phase was extracted with pet. ether (3×30 ml). The combined organic phase was washed with brine (40 ml) and dried (Na_2SO_4). Removal of solvent gave gummy product (0.221 g), the PMR spectrum of which showed formation of less than 50% of **4**; IR (film): 1745 (C=O) of enol acetate).

To the above mixture of **3** and **4** (0.221 g) was added DDQ (0.452 g, 2 mmol) in dry benzene (30 ml) and stirred for 24 hr at room temperature. The solution was filtered through neutral Al_2O_3 using benzene for washing. Further purification of the product, after removal of solvent, by TLC (SiO_2, pet. ether − ethyl acetate, 9:1) led to the recovery of the less polar **3** (0.17 g, 78% recovery), followed by the more polar **1** which solidified on keeping, as a yellow solid (0.01 g, 20% based on reacted material), m.p. 59° (from *n*-pentane) (lit.[1] 58.5-59°); UV (C_2H_5OH): 245 (log ε 4.18), 265 (3.93), 315 (3.32), 354 (3.48); IR ($CHCl_3$): 2960, 2920, 2880, 1650, 1550, 1380, 1300, 1130, 980, 890, 830; PMR($CDCl_3$): 1.27 [*d*, 6H, *J*=6.5 Hz, $CH(CH_3)_2$], 2.13 (*d*, 3H, *J*=1.5 Hz, vinylic CH_3), 2.68 (*s*, 3H, Ar−CH_3), 4.12 [*sept*, 1H, *J*=6.5 Hz, $CH(CH_3)_2$], 6.68 (*q*, 1H, *J*=1.5 Hz, vinylic C−H), 7.41 (*d*, 1H, *J*=8 Hz, Ar−H), 7.59 (*d*, 1H, *J*=8 Hz, Ar−H) (Found: C, 78.6; H, 7.2, Calc. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1%).

5-*Hydroxy*-4-*isopropyl*-1-*methyl*-6-*naphthaldehyde* (5-*Hydroxycadalenal*) (**7**)

To NaH (0.72 g, 50% mineral oil suspension, 15 mmol) in dry benzene (20 ml) a solution of **5**[2] (2.06 g, 10 mmol) in benzene (5 ml) was added and the mixture heated to reflux for 0.5 hr. After cooling to room temperature, ethyl formate (3 ml) was added and the stirring continued for 12 hr. After cooling (0°), it was quenched with AcOH (1 ml). Extractive work-up gave **6** as a gummy compound (2.2 g, 94%); IR(film): 1635, 1570; PMR (CCl_4): 1.23 [*d*, 6H, *J*=7 Hz, $CH(CH_3)_2$], 2.22 (*s*, 3H, Ar−CH_3) 2.27-2.83 [*m*, 4H, $(CH_2)_2$], 4.02 [*sept*, 1H, *J*=7 Hz $CH(CH_3)_2$], 7.13 (*s*, 2H, 2×Ar-H), 7.7 (*bd*, 1H, C=C*H*−OH, collapses into a singlet on exchange with D_2O), 14.8 (*b*, OH, exchangeable with D_2O).

To **6** (1.17 g, 5 mmol) in dry dioxan (15 ml) containing AcOH (0.8 ml), DDQ (1.13 g, 5 mmol) was added and the mixture stirred for 1 hr. It was filtered and the filtrate diluted with $CHCl_3$ (150

ml). The organic layer was washed with water (50 ml) and aq. $NaHCO_3$ (5%, 50 ml). Extractive work-up of the product, followed by filtration through neutral Al_2O_3 and purification by column chromatography (SiO_2, benzene-pet. ether, 2:3) gave **7** (0.85 g, yield 75%); m.p. 93° (from *n*-pentane): UV (C_2H_5OH): 224 (log ε 3.92) 258.5 (4.32), 263 (4.31), 292 (3.41), 303 (3.50), 315 (3.17), 390 (3.54): IR ($CHCl_3$): 3400, 1635, 1615, 1575, 1460, 1350, 1330, 1160, 1045, 835; PMR($CDCl_3$): 1.34 [*d*, 6H, J=7 Hz, $CH(CH_3)_2$], 2.6 (*s*, 3H, $Ar-CH_3$), 4.63 [*sept*, 1H, J=7 Hz, $CH(CH_3)_2$], 7.37 (*s*, 2H, 2×Ar−H), 7.42 (*s*, 2H, 2×Ar−H), 9.9 (*s*, 1H, CHO), 13.57 (*s*, OH, exchangeable with D_2O) (Found: C, 79.1; H, 7.1. $C_{15}H_{16}O_2$ requires C, 78.9; 7.1%).

Wolff-Kishner reduction of **7**

A mixture of **7** (0.466 g, 2 mmol), KOH pellets (2.5 g) and hydrazine hydrate (2.5 ml) in diethyleneglycol (15 ml) was heated under reflux for 2 hr. The temperature of the heating bath was raised to 200° and the heating continued for 6 hr. Extractive work-up gave **12** as a yellow solid (0.44 g, 96%); m.p. 220° (from $CHCl_3-CH_3OH$) (Found: C, 79.7; H, 7.2; N, 6.0. $C_{30}H_{32}N_2O_2$ requires C, 79.6; H, 7.1; N, 6.2%).

Sodium borohydride reduction of **7**

To a solution of **7** (0.114 g, 0.5 mmol) in aq. NaOH (1.22 *M*, 1 ml), water (2 ml) and ethanol (2 ml), $NaBH_4$ (0.04 g, 1 mmol) was added and the mixture heated at 70° for 1 hr. It was cooled (0°) and acidified carefully with 5*N* HCl to decompose the excess of $NaBH_4$. Extractive work-up, followed by TLC (SiO_2, benzene-pet ether, 2:3) gave **8** as a labile yellow liquid (0.1 g, 94%); IR (film); 3560; PMR(CCl_4): 1.31 [*d*, 6H, J=7 Hz, $CH(CH_3)_2$], 2.27 (*s*, 3H, $Ar-CH_3$), 2.53 (*s*, 3H, $Ar-CH_3$), 4.48 [*sept*, 1H, J=7 Hz, $CH(CH_3)_2$], 5.08 (*s*, OH, exchangeable with D_2O), 6.93-7.40 (*m*, 4H, 4×Ar−H).

Iodoxybenzene oxidation of **8** *to cadalenequinone* (**1**)

To **8** (0.05 g, 0.25 mmol) in acetic acid (1 ml), iodoxybenzene[9] (0.115 g, 0.5 mmol) was added under stirring. After stirring for 5 min, it was filtered and washed with ether (25 ml). Work-up of the organic phase, followed by purification of the product by TLC (SiO_2, benzene-pet. ether, 2:3) gave **1** which solidified on keeping as a yellow solid (0.045 g; 87%), identical with the specimen (m.p. and m.m.p.) obtained above by the route, **3** → **4** → **1**.

Acknowledgement

The authors thank the CSIR, New Delhi, for financial assistance and for the award of a senior research fellowship (to NKR).

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Chemical Transformations of Cyclotagitinin-C

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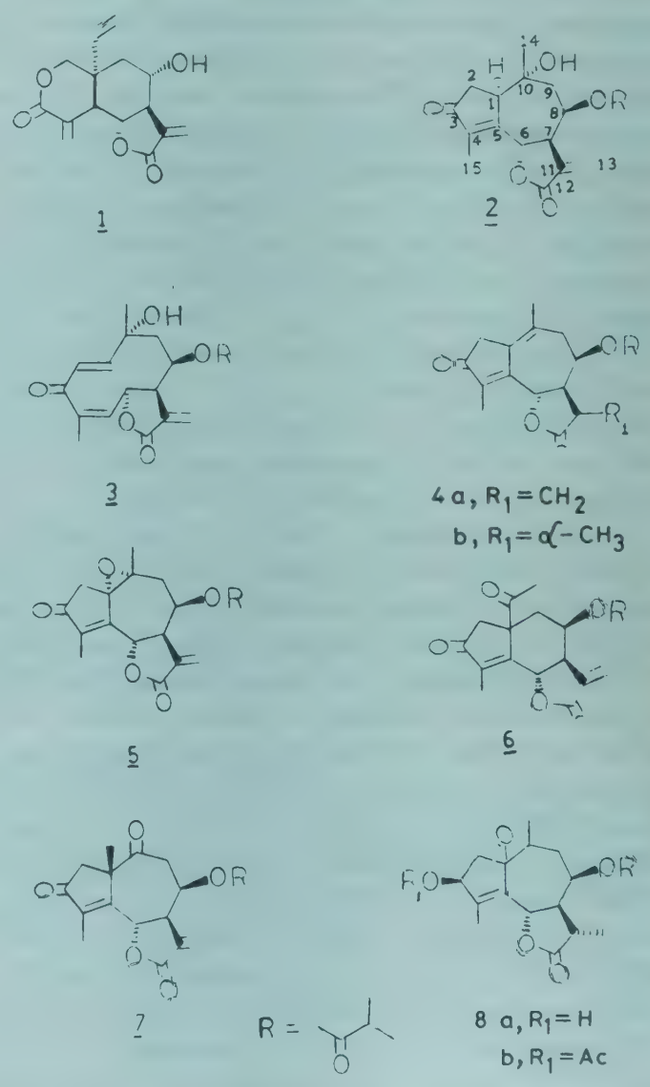
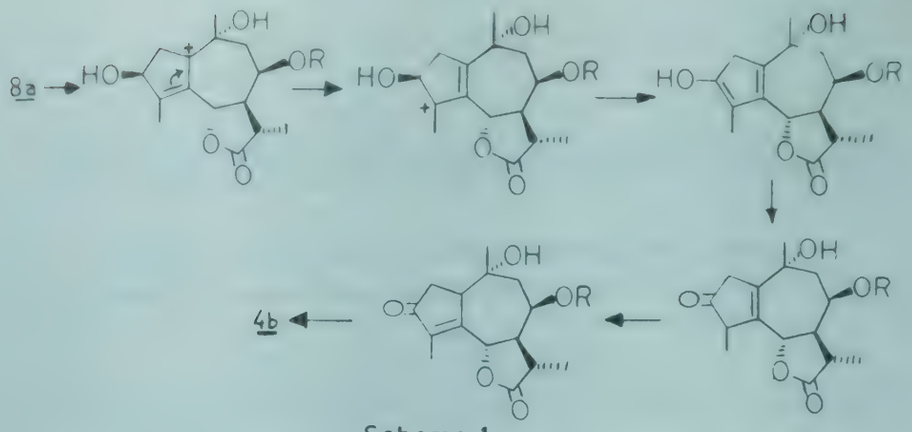
An attempt to convert cyclotagitinin-C (**2**) into vernolepin (**1**), though unsuccessful, has led to two other interesting transformations. Dehydrobromination of an α, β-unsaturated-α′-bromoketone (**10d**) with calcium carbonate in dimethylacetamide has furnished compound (**11a**). Reaction of the epoxy ketone (**16b**) with $SnCl_4.5H_2O$ has yielded compound **11b**.

Vernolepin (**1**) is a highly potent antileukemic sesquiterpene lactone isolated by Kupchan *et al*[1] in 1969 and since then it has been the subject of several total syntheses. A report on the transformation of santonin to **1** by Fujimoto *et al*[2] prompted us to study the conversion of cyclotagitinin-C (**2**) into **1**. Although our attempts did not turn out to be fruitful, nevertheless some interesting observations have been made which are presented in this paper.

In an earlier article it has been described that acid-catalysed cyclization of tagitinin-C (**3**) provides cyclotagitinin-C (**2**)[3]. When the epoxide (**5**) obtained from **2** via the dienone (**4a**) was reacted with $SnCl_4.5H_2O$ in refluxing benzene with the aim of getting the skeleton (**6**) for further elaboration to **1**, ketone (**7**) was obtained as the major product[4]. Since it is known that the course of epoxide rearrangement is highly dependent upon the presence of other functionalities in a molecule[5], it was decided to carry out these studies on another analogue of **5**. Sodium borohydride reduction of **5** furnished the alcohol (**8a**) which was acetylated to **8b**. Exposure of **8b** to various Lewis acids led to extensive decomposition and no useful product could be isolated. However, treatment of the dichloromethane solution of **8a** with a drop of conc. H_2SO_4 at 0° furnished **4b** as the major product whose formation has been rationalised as shown in Scheme 1.

Having failed to achieve the desired rearrangement through 10, 1-epoxide, it was decided to carry out these studies on 1,2-epoxide. Hydrogenation of **2** over 10% Pd-C for 4 hr at 22 psi resulted in the formation of two major products, the less polar product was identified as **9a** with C-13 methyl as α($J_{7,11}$ = 12.5 Hz)[6] and the more polar product was assigned structure (**9c**)($J_{7,11}$ = 9.5 Hz). As the signals due to H-4 and H-5 in **9a** and **9c** were masked by other proton signals, it was difficult to decide the stereochemistry of C-15 methyl at this stage. However, in some other transformation products (vide infra) the low $J_{4,5}$ value suggested it to be β. Isomerisation of the crude mix-



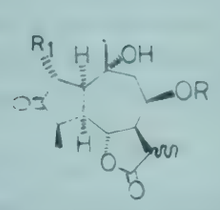


Scheme 1

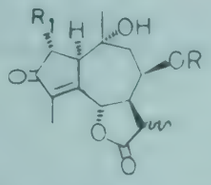
ture obtained by hydrogenation of **2** under basic conditions led to the formation of **9a** as the major product whereas isomerization of the same mixture under acidic conditions furnished **9c** as the major product.

With the aim of introducing a double bond in 1, 2-position of **9a**, it was brominated with bromine in acetic acid to yield a mixture consisting of **10a** and **10b**. Bromination of **9c** yielded a mixture of three products which were separated and identified as **10c**, **10d** and **9b**. Formation of these compounds can be rationalized as follows. Since bromination of a ketone takes place through its enol form[7], it appears that enolisation of the keto group in **9a** and **9c** is taking place in both the directions (i.e. C-2, C-3 double bond and C-3, C-4 double bond) with equal ease resulting in the introduction of bromine at C-2 or C-4 or at C-2 and C-4 both. Obviously C-4 bromo compounds are not stable and dehydrobromination occurs under the reactions to furnish **10a**, **10b**, **10c** and **10d**.

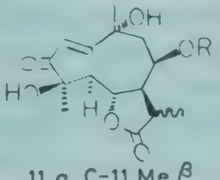
Dehydrobromination of **10d** with calcium carbonate in refluxing dimethylacetamide resulted in the formation of two hydrodebromination products (**10a**) and (**10c**) along with compound (**11a**). Compound (**11a**) was also isolated as the major product when **10d** was treated with a mixture of lithium bromide and lithium carbonate in refluxing dimethylformamide. The proof for the introduction of a hydroxyl at C-4 in **11a** and the β-stereochemistry assigned to it were forthcoming from its PMR spectrum in the presence of trichloroacetyl isocyanate (TAI)[8]. In the TAI spectrum, the methyls at C-10 and C-4 underwent paramagnetic shift to δ1.89 and 1.66 respectively confirming the presence of hydroxyl groups at these positions. The appearance of H-5 at 3.22 (diamagnetic shift) and that of H-6 at 4.99 (paramagnetic shift) suggested that the hydroxyl at C-4 is β. Although several mechanisms can be advanced to explain the formation of compound (**11a**), the most plausible one has been given in Scheme 2[9]. Treatment of **10b** with calcium carbonate in refluxing DMA furnishes the hydrodebromination product (**10a**). The reductive removal of



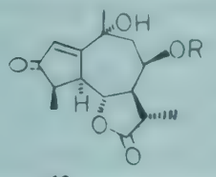
9 a, R_1=H, C-11 Me α
b, R_1=Br, C-11 Me β
c, R_1=H, C-11 Me β



10 a, R_1=H, C-11 Me α
b, R_1=Br, C-11 Me α
c, R_1=H, C-11 Me β
d, R_1=Br, C-11 Me β



11 a, C-11 Me β
b, C-11 Me α



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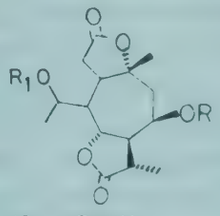
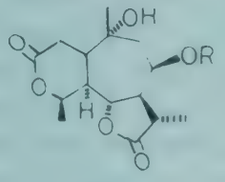


13 a, R_1=H
b, R_1=Ac



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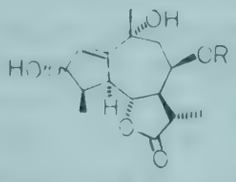
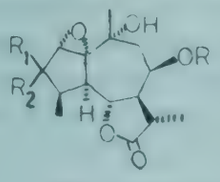


15 a, 3-OH α
b, 3-OH β

R=

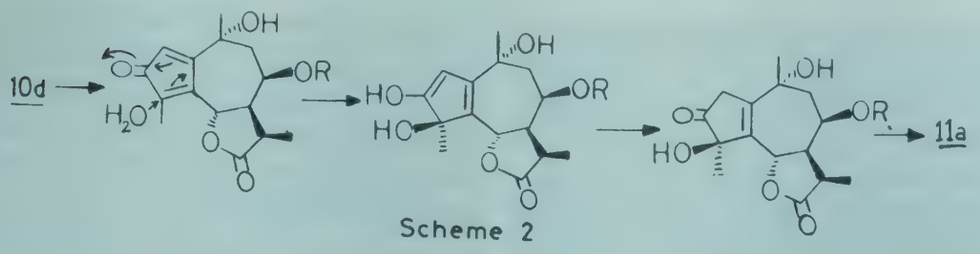


16 a, R_1=OH, R_2=H
b, R_1·R_2=O

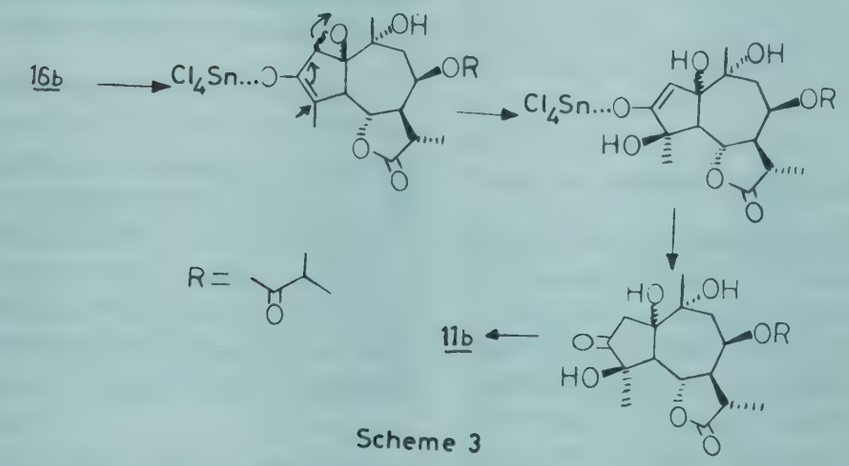
bromine under these conditions is certainly not intriguing[10].

Dehydrobromination of **9b** with calcium carbonate in refluxing DMA resulted in the formation of **12**. However, as the bromo compound (**9b**) and its dehydrobrominated product (**12**) were obtainable in poor yield, it was decided to abandon this scheme.

At this stage, a fortuitous observation led to the obtention of a compound containing 1, 2 double bond in good yield. In an attempt to study the Baeyer-Villiger



Scheme 2



Scheme 3

oxidation of **9a** under acidic conditions, it was treated overnight at room temperature with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of *p*-toluenesulphonic acid and one major compound (**12**) and three minor compounds (**10a**) (**13a**) and (**14**) were isolated.

The major product (**12**), obtained as a crystalline compound, m.p. 156-58°, analysed for $C_{19}H_{26}O_6$ in the high resolution mass spectrum. In its IR spectrum the presence of an absorption band at 1700 cm^{-1} suggested the introduction of a double bond in the cyclopentanone ring which was confirmed by its PMR spectrum therein H-2 appeared as a doublet (J= 2 Hz) at δ6.06 and therefore structure (**12**) was assigned to it. The introduction of a hydroxyl α to the carbonyl function has been reported under these conditions[11]. This is followed by dehydration to furnish **12**.

In the PMR spectrum of **14**, a one-proton doublet of quartets at δ5.13 (J= 1.5 and 7 Hz) and a low field three-proton doublet (J= 7 Hz) at 1.48 were consistent with the assigned structure. The β-stereochemistry to C-15 methyl was assigned on the basis of $J_{4,5}$ = 1.5 Hz (molecular models). Similarly, proof for the structure of **13a** was obtained from its PMR spectrum in which H-4 appeared as a quintent (J= 7 Hz) at δ4.26 and H-6 as a triplet (J= 10 Hz) at 4.51. Acetylation of **13a** gave **13b** in the PMR spectrum of which H-4 underwent paramagnetic shift and appeared at δ5.33.

Compound (**12**) did not react with H_2O_2 or *m*-CPBA under basic conditions, therefore it was reduced with sodium borohydride to furnish a mixture of two diols (**15a**) and (**15b**). The PMR spectrum of the two diols were essentially identical except the multiplicity of the proton at C-3 and it was difficult to distinguish the two isomers on the basis of multiplicity of H-3. However, as our intention was to oxidise the hydroxyl at C-3 to carbonyl group at a later stage, the crude mixture of the two diols (**15a**) and (**15b**) was treated with *m*-CPBA and the epoxide (**16a**) was isolated as the major product. Oxidation of **16a** with Collins' reagent[12] furnished the ketone (**16b**). Exposure of **16b** to $SnCl_4.5H_2O$ in refluxing benzene furnished **11b** as the sole product. Formation of **11b** has been rationalised as shown in Scheme 3. This is the fourth example of a potentially useful method for effecting a nucleophilic attack at the α′-site of an α, β-unsaturated ketone[13-15].

Experimental Procedure

Melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded in $CHCl_3$ on a Perkin-Elmer 237B grating IR spectrophotometer and PMR spectra in $CDCl_3$ on either Varian T-60 or Bruker HX-270 MHz instrument; chemical shifts are given in δppm, with TMS as internal reference. Low resolution MS and high resolution MS were recorded on MS-30 and MS-902 instruments respectively.

Sodium borohydride reduction of **5**: *Formation of alcohol* (**8a**)

To a stirred solution of **5** (50 mg) in methanol (5 ml) was added sodium borohydride (50 mg) at 5°. The reaction mixture was diluted with water, acidified

with dil acetic acid and extracted with chloroform. The washed and dried extract was evaporated under reduced pressure and the residue purified by preparative TLC (EtOAc-Bz, 1:3) to yield **8a** as a gum (21 mg). It was characterised as its acetate **8b** also obtained as a gum; IR: 1775, 1740 (very strong), 1230 and 1120 cm^{-1}; PMR (60 MHz); 5.50 (*m*, H-3, H-6 and H-8), 4.30 (*m*, H-7), 1.22 (d, *J*= 7 Hz, H-13), 1.46 (H-14), 1.88 (*br*, H-15), 1.12 (*d*, *J*= 7 Hz, H-3′ and H-4′) and 2.14 (OAc); MS: *m/z* 392 (M^+), 348, 304, 277, 260, 244 and 71.

Reaction of **8a** *with conc.* H_2SO_4*: Formation of* **4b**

A solution of **8a** (50 mg) in dichloromethane (5 ml) was cooled to 0° and treated with 2 drops of conc. sulfuric acid with shaking. After 10 min, the reaction mixture was kept at 5° for 2 hr, diluted with excess water, extracted with dichloromethane, the organic extract washed with water and dried (Na_2SO_4). Concentration of the extract under reduced pressure left a residue which on purification by preparative TLC (EtOAc-Hexane, 1:2) furnished **4b** as a gum (34 mg); IR: 1775, 1730, 1700, 1150, 1070 and 1010 cm^{-1}; PMR (60 MHz): 5.40 (*m*, H-6 & H-8), 1.28 (*d*, *J*= 7 Hz, H-13), 2.00 (H-14), 2.10 (H-15), 1.20 (*d*, *J*= 7 Hz, H-3′ and H-4′); MS: *m/z* 332 (M^+) 261, 244, 229 and 71.

Hydrogenation of cyclotagitinin-C (**2**)*: Formation of* **9a** *and* **9c**

A solution of **2** (100 mg) in absolute ethanol (25 ml) was hydrogenated over Pd-C (100 mg, 10%) at 22 psi for 4 hr, filtered and the filtrate evaporated under reduced pressure to furnish a residue which on purification by preparative TLC (EtOAc-Hexane, 1:1) yielded **9a** as a gum (50 mg) and **9c** as solid (25 mg), m.p. 133-34° (EtOAc). IR of **9a**: 3500, 1775, 1740, 1730, 1150 and 1000 cm^{-1}; PMR (270 MHz, C_6D_6): 1.76 (H-1), 2.09 (*m*, H-2 & H-4), 1.76 (*m*, H-5), 3.87 (*t*, *J*= 10 Hz, H-6), 2.16 (*m*, H-7), 5.19 (*dt*, *J*= 3.5 & 6.5 Hz, H-8), 1.61 (*dd*, *J*= 15 & 6.5 Hz, H-9a) and 1.46 (*dd*, *J*= 15 & 6.5 Hz, H-9b), 2.36 (*dq*, *J*= 12.5 & 7 Hz, H-11), 1.11 (*d*, *J*= 7 Hz, H-13), 0.63 (H-14), 1.12 (*d*, *J*= 7.5 Hz, H-15), 2.25 (*sept*, H-2′), 0.99 (*d*, *J*= 7 Hz, H-3′) and 0.98 (*d*, *J*= 7 Hz, H-4′); MS: *m/z* (%) 352 (M^+), 334 (11.5), 264 (11.4), 246 (9.5) and 71 (100); calc. for $C_{19}H_{28}O_6$. mol wt 352.1886; Found: 352.1886 (MS).

IR of **9c**: 3500, 1775, 1740, 990 and 930 cm^{-1}; PMR (270 MHz): 2.59 (H-1), 2.84 (*m*, H-2), 2.36 (*m*, H-4), 2.36 (*m*, H-5), 4.85 (*dd*, *J*= 10 & 9 Hz, H-6), 2.97 (*bt*, *J*= 9.5 Hz, H-7), 5.39 (*bt*, *J*= 3.5 Hz, H-8), 2.17 (*dd*, *J*= 15 & 3.5 Hz, H-9a) and 1.98 (*dd*, *J*= 15 & 3.5 Hz, H-9b), 2.87 (*br*, H-11), 1.19 (*d*, *J*= 7 Hz, H-13), 1.22 (H-14), 1.27 (*d*, *J*= 7.5 Hz, H-15), 2.54 (*sept*, *J*= 7 Hz, H-2′), 1.20 (*d*, *J*= 7 Hz, H-3′ and H-4′); MS: *m/z* (%) 352 (M^+), 334 (6.7), 264 (6.9), 246 (5.3) and 71 (100); calc. for $C_{19}H_{28}O_6$ mol wt 352.1886; found 352.1886 (MS).

Isomerisation of hydrogenated product of **2** *with sodium carbonate: Formation of* **9a**

A solution of crude hydrogenated product (100 mg) of **2** in ethanol (10 ml) was treated with sodium carbonate (200 mg). The reaction mixture was stirred for 45 hr at room temperature, diluted with excess water and extracted with chloroform (3 × 50 ml). The combined extract was washed with water, dried (Na_2SO_4), solvent removed under reduced pressure and the residue purified by preparative TLC (EtOAc-Hexane, 1:1) to afford **9a** as a gum (70 mg).

Isomerisdtion of hydrogenated product of **2** *with perchloric acid: Formation of* **9c**

A solution of the crude hydrogenated product (100 mg) of **2** in perchloric acid (10 ml, 60-62%) was left overnight at room temperature, diluted with water and extracted with chloroform (3 × 50 ml). The washed and dried extract was distilled under reduced pressure to get a residue which was purified by preparative TLC (EtOAc-Hexane, 1:1) to furnish **9c** as a solid (70 mg), m.p. and m.m.p. 133-34°.

Bromination of **9a**

A solution of **9a** (50 mg) in chloroform (5 ml) was treated at room temperature with 10 drops of glacial acetic acid and 25 drops of bromine in chloroform (prepared by adding 10 drops of Br_2 in 5 ml $CHCl_3$). The reaction mixture was stirred at room temperature for 15 min, diluted with chloroform, washed with water followed by hypo solution. Evaporation of the dried extract under reduced pressure left a residue which was purified by preparative TLC ((EtOAc-hexane, 1:2) to furnish **10a** as a solid (10 mg), m.p. 217-19° (Hexane-EtOAc) and **10b** as a gum (25 mg). IR of **10a**: 3500, 1775, 1725, 1700, 1625, 1125, 990, 950, 935 and 775 cm^{-1}; PMR: (270 MHz): 3.31 (*m*, H-1), 2.60 (H-2a & 2b), 5.29 (*bd*, *J*= 10 Hz, H-6), 2.45 (H-7), 5.44 (*bt*, *J*= 7 Hz, H-8), 240 (H-9a) and 2.03 (*bdd*, *J*= 15 & 3.5 Hz, H-9b), 2.40 (H-11), 1.33 (*d*, *J*= 7 Hz, H-13), 1.09 (H-14), 1.95 (*t*, *J*= 1.5 Hz, H-15), 2.62 (sept, *J*= 7 Hz) HH-2′), 1.23 (*d*, *J*= 7 Hz, H-3′) and 1.24 (*d*, *J*= 7 Hz, H-4′); MS: *m/z* (%) 350 (2.8), 280 (8.4), 262 (23) and 71 (100); calc. for $C_{19}H_{26}O_6$ mol wt 350.1727; found: 350.1729 (MS).

IR of **10b**: 3500, 1775, 1735, 1710, 1220, 1140 and 995 cm^{-1}; PMR (270 MHz):3.48 (*bq*, *J*= 2 Hz, H-1), 4.56 (*dd*, *J*= 2 & 1 Hz, H-2), 5.26 (*bd*, *J*= 11 Hz, H-6), 5.43 (*bt*, *J*= 3.5 Hz, H-8), 1.31 (*d*, *J*= 7 Hz, H-13), 1.07 (H-14), 2.02 (*t*, *J*= 2 Hz, H-15), 2.61 (*sept*, *J*= 7 Hz, H-2′) and 1.21 (*d*, *J*= 7 Hz, H-3′ and H-4′); H-7, 9 & 11 appeared as a complex multiplet. The low resolution mass spectrum did not exhibit the molecular ion peak but other major peaks were at *m/z* 348, 278, 260 and 71.

Bromination of **9c**

A solution of **9c** (50 mg) in chloroform (5 ml) was brominated as described above. Usual work-up and purification by preparative TLC (EtOAc-hexane, 1:2) furnished **9b** as a gum (5 mg), **10c** as a solid m.p. 238-39° (hexane-$CHCl_3$) and **10d** as a gum (20 mg); IR of **9b**: 1775, 1730, 1640, 1150 and 990 cm^{-1}; PMR (270 MHz): 2.32 (*m*, H-1), 4.88 (*br*, H-2), 2.53 (*m*, H-5), 4.92 (*dd*, *J*= 10 & 9 Hz, H-6), 2.76 (*bt*, *J*= 9 Hz, H-7), 5.39 (*bt*, *J*= 3.5 Hz, H-8), 2.29 (*dd*, *J*= 15 & 3.5 Hz, H-9a), 1.90 (*bdd*, *J*= 15 & 3.5 Hz, H-9b), 2.87 (*dq*, *J*= 9 & 7.5 Hz, H-11) 1.20 (*d*, *J*= 7 Hz, H-13), 1.16 (H-14), 1.52 (*d*, *J*= 7 Hz, H-15), 2.53 (*sept*, *J*= 7 Hz, H-2′) and 1.19 (*d*, *J*= 7 Hz, H-3′ and H-4′); MS: *m/z* 432 and 430 (M^+), 351, 350, 280, 263 and 71 (100).

IR of (**10c**): 3600, 1775, 1730, 1700, 1625, 1140, 1000 and 935 cm^{-1}; PMR (270 MHz): 3.37 (*m*, H-1), 2.61 (H-2a & 2b, centre of *AB* part of *ABX* system), 5.57 (*bd*, *J*= 12 Hz, H-6), 3.01 (*bdd*, *J*= 11.5 & Hz, H-7), 5.50 (*bt*, *J*= 3.5 Hz, H-8), 2.37 (*dd*, *J*= 15 & 3.5 Hz, H-9a) and 1.99 (*bdd*, *J*= 15 & 3.5 Hz, H-9b) 2.85 (*dq*, *J*= 8 & 7 Hz, H-11), 1.34 (*d*, *J*= 7 Hz, H-13), 1.03 (H-14), 1.97 (*t*, *J*= 1.5 Hz, H-15), 2.56 (*sept*, *J*= 7 Hz, H-2′) and 1.21 (*d*, *J*= 7 Hz, H-3′ and H-4′); MS: *m/z* (%) 350 (M^+, 0.8), 280 (60), 262 (27.7) and 71 (100); calc. for $C_{19}H_{26}O_6$: mol wt 250.1727; found: 250.1733 (MS).

IR of (**10d**): 3575, 1780, 1740, 1720, 1640, 1130, 1100 and 990 cm^{-1}; PMR (270 MHz): 3.57 (*m*, H-1), 4.59 (*bd*, *J*= 2 Hz, H-2), 5.57 (*bd*, *J*= 11 Hz, H-6), 2.98 (*bdd*, *J*= 11.5 & 8 Hz, H-7), 5.50(*bt*, *J*= 3.5 Hz, H-8), 2.39 (*dd*, *J*= 15 & 3.5 Hz, H-9a) and 2.12 (*bdd*, *J*= 15 &3.5 Hz, *H*-9*b*), 2.85 (*quintet*, *J*= 8 Hz, H-11), 1.22 (*d*, *J*= 7 Hz, H-13), 1.02 (*br*, H-14), 2.13(*br*, H-15), 2.54 (*sept*, *J*= 7 Hz, H-2′), 1.20 (*d*, *J*= 7 Hz, H-3′ and H-4′); MS:*m/z* (%) 349 (M^+-Br, 2.8), 348 (2.9), 278(9), 261 (100) and 71 (62.5).

Reaction of **10d** *with calcium carbonate-dimethylacetamide. Formation of* **10a, 10c** *and* **11a**

Compound (**10d**, 100 mg) was added portionwise to calcium carbonate (85 mg) in boiling dimethylacetamide (4 ml) during 3 min and refluxing was continued for 6 hr. The reaction mixture was cooled, excess water added and extracted with chloroform. The washed and dried extract on evaporation under reduced pressure yielded a residue which on purification by preparative TLC (EtOAc-hexane, 1:1) furnished **10a** as a solid (8 mg), m.p. 217-19° (hexane-EtOAc), (**10c**) (30 mg), m.p.238-39° (hexane-chloroform) and **11a** as a gum (15 mg); IR of **11a**: 3500, 1775, 1725 (doubly intensity), 1175, 1000 and 925 cm^{-1}; PMR (270 MHz): 6.08 (*d*, *J*= 2 Hz, H-2), 3.53 (*dd*, *J*= 9 Hz, & 2 Hz, H-5), 4.77 (*dd*, *J*= 10.5 & 9 Hz, H-6), 3.61 (*dd*, *J*= 10.5 & 8 Hz, H-7), 5.29 (*bd*, *J*= 6.5 Hz, H-8), 2.49 (*dd*, *J*= 15 & 6.5 Hz, H-9a), 1.79 (*bd*, *J*= 15 Hz, H-9b), 2.72 (*quint*, *J*= 7 Hz, H-11), 1.11 (*d*, *J*= 7.5 Hz, H-13), 1.60 (H-14), 1.46 (H-15), 2.41 (*sept*, *J*= 7 Hz, H-2′) and 1.07 (*d*, *J*= 7 Hz, H-3′ and H-4′; PMR (with TAI): 6.33 (*d*, H-2), 3.22 (*dd*, *H*-5), 4.99 (*t*, *J*= 10 Hz, H-6), 3.19 (*dd*, H-7), 5.34 (*bd*, H-8), 2.91 (*dd*, H-9a), 1.79 (*bd*, H-9b), 2.78 (*quint*, H-11), 1.09 (*d*, H-13), 1.89 (H-14), 1.66 (H-15), 2.64 (*sept*, H-2′), 1.14 (*d*, H-3′), 1.13 (*d*, H-4′), 8.58, 8.39 (NH); MS:*m/z* (%) 366 (M^+), 348 (0.6), 295 (0.7), 278 (6.2), 260 (23.7) and 71 (100); calc. for $C_{14}H_{26}O_7$: mol wt 366.1676; found: 366.1686 (MS).

Reaction of **10d** *with lithium carbonate-lithium bromide in dimethylformamide. Formation of* **11a**

A solution of **10d** (50 mg) in dry dimethylformamide (5 ml) was refluxed at 160° under N_2 atmosphere with a mixture of lithium carbonate (50 mg) and lithium bromide (60 mg) for 18 hr. The reaction mixture was cooled, diluted with water, extracted with chloroform, the extract was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by preparative TLC (EtOAc-hexane, 1:1) yielded **11a** as gum (23 mg).

Reaction of **10b** *with calcium carbonate—dimethylacetamide. Formation of* **10a**

Compound (**10b,** 100 mg) was added portionwise to calcium carbonate (85 mg) in boiling dimethylacetamide (4 ml) during 3 min and refluxing was contained for 6 hr. Usual work-up and purification by preparative TLC (EtOAc-hexane, 1:1) yielded **10a** as a crystalline solid (45 mg), m.p. 217-19° (hexane-EtOAc).

Dehydrobromination of **9b**: *Formation of* **12**

Compound (**9b**, 25 mg) was added portionwise to calcium carbonate (22 mg) in boiling dimethylacetamide (3 ml) during 3 min and refluxing was continued for 6 hr. Usual work-up of the reaction mixture and purification by preparative TLC (EtOAc-hexane, 1:4) furnished **12** as a crystalline solid (3 mg), m.p. 156-58° (EtOAc-$CHCl_3$).

Bayer-Villiger oxidation of **9a** *in presence of TsOH: Formation of* **10a** *and* **12-14**

To a solution of (**9a**, 100 mg) in chloroform (5 ml) was added *m*-CPBA (100 mg) and TsOH (10 mg). The reaction mixture was left at room temperature overnight, diluted with chloroform, washed once with aq. potassium iodide and liberated iodine was destroyed by washing with aq. sodium thiosulphate. The chloroform solution was washed with diluted aq. sodium bicarbonate followed by water and dried (Na_2SO_4). Distillation under reduced pressure left a residue which on purification by preparative TLC (24% MeOH-$CHCl_3$) furnished **12** (45 mg), **10a** (4 mg, m.p. 217-19°) (hexane-EtOAc), **13a** (9 mg) and (**14**) as a gum (3 mg). Compound (**12**) was crystallised from ethanol-chloroform, m.p. and m.m.p. 156-58°. Ir of **12**: 3500, 1775, 1730, 1700, 1605, 1150 and 1000 cm^{-1}; PMR (270 MHz): 6.06 (*d*, *J* = 2 Hz, H-2), 2.52 (*bq*, *J* = 7 Hz, H-4), 2.97 (*td*, *J* = 2 & 10.5 Hz, H-5), 4.14 (*t*, *J* = 10.5 Hz, H-6), 3.09 (*ddd*, *J* = 12, 10.5 & 4.5 Hz, H-7), 5.37 (*ddd*, *J* = 9, 6 & 4.5 Hz, H-8), 2.76 (*dd*, *J* = 15 & 9 Hz, H-9a), 1.54 (*dd*, *J* = 15 & 6 Hz, H-9b), 2.55 (*m*, H-11), 1.30 (*d*, *J* = 7 Hz, H-13), 1.64 (H-14), 1.25 (*d*, *J* = 7.5 Hz, H-15), 2.60 (*sept*, *J* = 7 Hz, H-2′), 1.16 (*d*, *J* = 7 Hz, H-3′) and 1.15 (*d*, *J* = 7 Hz, H-4′); PMR with TAI: 6.23 (*d*, H-2). 2.59 (*bq*, H-4), 2.65 (*td*, H-5), 4.13 (*t*, H-6), 2.79 (*ddd*, H-7), 5.49 (*ddd*, H-8), 3.11 (*dd*, H-9a) and 1.71 (*dd*, H-9b), 2.59 (*m*, H-11), 1.29 (*d*, H-13), 1.92 (H-14), 1.26 (*d*, H-15), 2.59 (*sept*, H-2′), 1.18 (*d*, H-3′), 1.17 (*d*, H-4′) and 8.24 (NH); MS: *m/z* (%) 350 (M^+), 332 (3.1), 280 (14.4), 262 (23.8), 244 (60.5) and 71 (100); calc. for $C_{19}H_{26}O_6$: mol wt 350.1729; found: 350.1729 (MS). IR of **13a**: 3500, 1775, 1750, 1735, 1710, 1250, 1150, 1050, 995 and 960 cm^{-1}; PMR (270 MHz): 2.86 (*dd*, *J* = 13 & 7.5 Hz, H-1), 3.36 (*dd*, *J* = 16.5 & 13 Hz, H-2a), 2.60 (*dd*, *J* = 16.5 & 7.5 Hz, H-2b), 4.26 (*quint*, *J* = 7 Hz, H-4), 2.11 (*ddd*, *J* = 10, 7.5 Hz, H-5), 4.51 (*t*, *J* = 10 Hz, H-6), 2.34 (*m*, H-7), 5.41 (*bt*, *J* = 3 Hz, H-8), 2.49 (*dd*, *J* = 15 & 3 Hz, H-9a), 1.94 (*dd*, *J* = 15 & 3.5 Hz, H-9b), 2.34 (*m*, H-11), 1.27 (*d*, *J* = 7 Hz, H-13), 1.49 (H-14), 1.41 (*d*, *J* = 7 Hz, H-15), 2.60 (*m*, H-2′) and 1.21 (*d*, *J* = 7 Hz, H-3′ and H-4′); MS: *m/z* 368 (M^+), 350 (M^+-18), 324, 280, 262 and 71 (100).

Compound (**13a**) was converted in the usual way into its acetate (**13b**).

IR of **14**: 3575, 1775, 1725 (double intensity), 1125 and 990 cm^{-1}; PMR (270 MHz); 2.3-2.6 (complex *m*, H-1, H-2, H-5, H-9a, H-11 and H-2′), 5.13 (*dq*, *J* = 1.5 & 7 Hz, H-4), 4.46 (*t*, *J* = 10.5 Hz, H-6), 2.87 (*ddd*, *J* = 14, 10.5 & 3.5 Hz, H-7), 5.28 (*ddd*, *J* = 9, 4 & 3.5 Hz, H-8), 1.69 (*bdd*, *J* = 15 & 4 Hz, H-9b), 1.23 (*d*, *J* = 7 Hz, H-13), 1.37 (H-14), 1.48 (*d*, *J* = 7 Hz, H-15), 1.18 (*d*, *J* = 7 Hz, H-15), 1. 18 (*d*, *J* = 7 Hz, H-3′ and H-4′); MS: *m/z* (%) 368 (M^+ very weak), 297 (2.4), 280 (7.2), 262 (8.9) and 71 (100); calc. for $C_{19}H_{28}O_7$ mol wt 368.1883; found: mol wt 368.1835 (MS).

Sodium borohydride reduction of **12**: *Formation of* **15a** *and* **15b**

A solution of **12** (50 mg) in methanol (5 ml) was stirred at 0° with sodium borohydride (50 mg) for 15 min. Usual work-up and purification by preparative TLC (EtOAc-hexane, 1:1) furnished **15a** (22 mg) and **15b** (17 mg) as gums. IR of **15a**: 3500, 1775, 1730, 1220, 1160 and 1000 cm^{-1}; PMR (270 MHz): 5.74 (*t*, *J* = 2 Hz, H-2), 4.36 (*m*, H-3), 2.20-2.80 (complex *m*, H-4 , H-5, H-9, H-11 and H-2′), 4.25 (*t*, *J* = 10 Hz, H-6), 2.94 (*ddd*, *J* = 12.5, 10 & 4 Hz, H-7), 5.32 (*dt*, *J* = 4 & 8 Hz, H-8), 1.26 (*d*, *J* = 7 Hz, H-13), 1.56 (H-14), 1.22 (*d*, *J* = 7 Hz, H-15), 1.16 (*d*, *J* = 7 Hz, H-3′ and H-4′); MS: *m/z* (%) 264 (M^+-88, 5.2), 246 (11.4), 148 (38.5) and 71 (100); MS: *m/z* (CI) 353 (M^+ + 1, 100), 335 (35.1), 265 (8.1) and 247 (57.1); calc. for $C_{19}H_{28}O_6$: mol wt 352.1884; found: 352.1893 (MS).

IR **15b**: 3500, 1775, 1730, 1220, 1160, 1090 and 1000 cm^{-1}; PMR (270 MHz): 5.80 (*t*, *J* = 2 Hz, H-2), 4.73 (*ddd*, *J* = 6.5, 2 & 2 Hz, H-3), 2.80 (*dddd*, *J* = 10, 5.5, 2 & 2 Hz, H-5), 4.12 (*t*, *J* = 10 Hz, H-6), 2.96 (*ddd*, *J* = 12.5, 10 & 4 Hz, H-7), 5.32 (*dt*, *J* = 4 & 8 Hz, H-8), 2.22-2.72 (*m*, H-9a, H-11 and H-2′), 1.22 (*d*, *J* = 7 Hz, H-13), 1.57 (H-14), 1.22 (*d*, *J* = 7 Hz, H-15) and 1.16 (*d*, *J* = 7 Hz, H-3′ and H-4′); MS: *m/z* 352 (0.5), 334 (10.5), 282 (1.5), 264 (14.6), 246 (14.3), 190 (12.8), 175 (12.2), 173 (12.2), 168 (14.2), 161 (10.3) and 71 (100); MS (CI): 353 (M^+ + 1, 100), 335 (32.1), 265 (15.6), 247 (10.4) and 169 (47.2); calc. for $C_{19}H_{28}O_6$: mol wt 352.1884; found: 352.1893 (MS).

Epoxidation of **15**: *Formation of* **16a**

A solution of mixture (50 mg) of **15a** and **15b** in chloroform (3 ml) was treated with *m*-CPBA (50 mg), the reaction mixture kept at room temperature overnight, diluted with chloroform, washed with aq. potassium iodide followed by aq. sodium thiosulphate and water. The dried extract was evaporated under reduced pressure to furnish a residue which on purification by preparative TLC (EtOAc-hexane, 1:1) yielded **16a** (14 mg) and an inseparable mixture (17 mg) of two compounds (PMR). IR of **16a**: 3500, 1775, 1735, 1140, 1120 and 995 cm^{-1}; PMR (270 MHz): 3.62 (*b*, H-2), 3.74 (*bd*, *J* = 8 Hz, H-3), 2.30-2.70 (*m*, H-4 and H-11), 2.20 (*dd*, *J* = 10 & 8 Hz, H-5), 4.48 (*t*, *J* = 10 Hz, H-6), 2.86 (*ddd*, *J* = 12.5, 10 & 4 Hz, H-7), 5.30 (*ddd*, *J* = 9, 6 & 4 Hz, H-7), 5.30 (*ddd*, *J* = 9, 6 & 4 Hz, H-8), 2.44 (*dd*, *J* = 15 & 9 Hz, H-9a), 1.82 (*dd*, *J* = 15 & 6 Hz, H-9b), 1.24 (*d*, *J* = 7 Hz, H-13), 1.19 (H-14), 1.26 (*d*, *J* = 7 Hz, H-15), 2.60 (*sept*, *J* = 7 Hz, H-2′) and 1.17 (*d*, *J* = 7 Hz, H-3′ and H-4′); MS: *m/z* (%) 368 (0.07), 280 (3.4) and 71 (100); calc. for $C_{19}H_{28}O_7$: mol wt 368.1833; found: 368.1838 (MS).

Oxidation of **16a**: *formation of* **16b**

A solution of **16a** (50 mg) in dichloromethane (4 ml) was treated with excess Collins' reagent[12] at − 10°. The reaction mixture was stirred and monitored by TLC. After completion of the reaction, the excess reagent was destroyed by adding a few drops of methanol and the reaction mixture diluted with dichloromethane (200 ml). Distillation of the washed and dried extract under reduced pressure left a residue which was purified by preparative TLC (EtOAc-hexane, 1:1) to yield **16b** as a gum (32 mg); IR: 3500, 1775, 1740, 1730, 1150 and 1120 cm^{-1}; PMR (270 MHz): 3.53 (H-2), 2.20-2.80 (*m*, H-4, H-5, H-9a, H-11) and H-2′), 4.64 (*t*, *J*= 10 Hz, H-6), 2.92 (*ddd*, *J*= 12.5, 10 & 4 Hz, H-7), 5.34 (*m*, H-8), 1.88 (*dd*, *J*= 15 & 6 Hz, H-9b), 1.24 (*d*, *J*= 7 Hz, H-13), 1.23 (H-14), 1.26 (*d*, *J*= 7 Hz, H-15), 1.20 (*d*, *J*= 7 Hz, H-3′ and H-4′); MS: *m/z* (%) 366 (0.07), 278 (10.8) and 71 (100); calc. for $C_{19}H_{26}O_7$: mol wt 366.1676; found: 366. 1668 (MS).

Reaction of **16b** *with* $SnCl_4$: *Formation of* **11b**

A solution of **16b** (20 mg) in dry benzene (3 ml) was treated with $SnCl_4.5H_2O$ (20 mg). The reaction mixture was refluxed for 10 hr on a water-bath, excess water was added and extracted with chloroform. The washed and dried extract was distilled under reduced pressure and the residue on purification by preparative TLC (EtOAc-hexane, 1:1) furnished **11b** as a gum (8 mg); IR: 3500, 1775, 1725 (double intensity), 1175, 995 and 925 cm^{-1}; PMR (270 MHz): 6.10 (*d*, *J*= 1.5 Hz, H-2), 3.28 (*dd*, *J*= 10.5 & 1.5 Hz, H-5), 4.56 (*t*, J = 10.5 Hz, H-6), 3.16 (*ddd*, *J*= 12, 10.5 & 4 Hz, H-7), 5.55 (*m*, H-8), 2.73 (*dd*, *J*= 15 & 9 Hz, H-9), 2.36 (*quint*, *J*= 7.5 Hz, H-11), 1.12 (*d*, *J*= 7.5 Hz, H-13), 1.66 (H-14), 1.48 (H-15), 2.54 (*sept*, *J*= 7 Hz, H-2′), 1.16 (*d*, *J*= 7 Hz, H-3′) and 1.14 (*d*, *J*= 7 Hz, H-4′); MS: *m/z* 366(M^+), 348, 295, 278, 260 and 71; calc. for $C_{19}H_{26}O_7$: mol wt 366.1676; found: 366.1682 (MS).

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Photochemical Synthesis of Benzothiazoles

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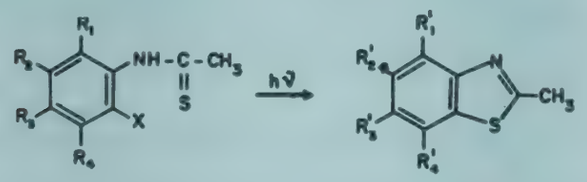
Irradiation of *o*-halothioacetanilides (**1a-p**) affords benzothiazoles (**2a-p**) in general. In methanol medium, polyhalogenated thioacetanilides yield benzothiazoles with the loss of bromine atom in the 4- or 6-position of the benzothiazole. Arylation of benzothiazoles occurs in benzene medium.

In a preliminary communication, we have reported[1] that irradiation of 2,3-dichlorothioacetanilide affords 7-chloro-2-methylbenzothiazole. In continuation of the above work, we report here the results of our study on the irradiation of *o*-chloro/bromothioacetanilides (**1**) (Scheme 1). In all the cases, dehydrohalogenation took place smoothly on irradiation affording the respective benzothiazole. However, dehydrobromination was predominant over dehydrochlorination as in the case of **1f-h**. Further, the reaction period was found to be less in the case of *o*-bromothioanilides. The only exception noted was 2,4,6-trichlorothioacetanilide (**1p**) which required almost the same reaction period as that of the tribromoanilide (**1i**).

Most of the anilides (**1**; Table 1) used in the present study contained more than one type of halogen. Anilides having only chlorine, on photolysis gave the respective benzothiazoles. However, if there was a bromine atom in a position other than the *ortho*, the photolysis (in methanol) products were the ex-



1 2

	R_1	R_2	R_3	R_4	X		R'_1	R'_2	R'_3	R'_4
a	-	-	-	-	Cl	(a)	-	-	-	-
b	-	-	-	Cl	Cl	(b)	-	-	-	Cl
c	-	-	Cl	-	Cl	(c)	-	-	Cl	-
d	-	-	Br	-	Cl	(d)	-	-	Br	-
e	-	-	Br	Cl	Cl	(e)	-	-	-	Cl
f	Cl	-	Br	-	Br	(f)	Cl	-	-	-
						(f')	Br	-	C_6H_5	-
						(f'')	Cl	-	C_6H_5	-
g	Cl	Cl	Br	-	Br	(g)	Cl	Cl	Br	-
						(g')	Cl	Cl	-	-
h	Cl	-	Cl	-	Br	(h)	Cl	-	Cl	-
i	Br	-	Br	-	Br	(i)	Br	-	Br	-
j	Br	-	Cl	-	Br	(j)	Br	-	Cl	-
						(j')	-	-	Cl	-
k	CH_3	Cl	Br	-	Br	(k)	CH_3	Cl	Br	-
						(k')	CH_3	Cl	-	-
l	CH_3	-	Br	Cl	Br	(l)	CH_3	-	-	Cl
m	Br	CH_3	Br	-	Br	(m)	Br	CH_3	Br	-
						[(m')	Br	-	Br	CH_3]
n	Br	-	CH_3	-	Br	(n)	Br	-	CH_3	-
						(n')	-	-	CH_3	-
o	C_6H_5	-	Br	-	Br	(o)	C_6H_5	-	Br	-
						(o')	C_6H_5	-	C_6H_5	-
p	Cl	-	Cl	-	Cl	(p)	Cl	-	Cl	-

2a' = 2b; 2j' = 2c; 2p = 2h

SCHEME 1

Table 1—Characterization Data of Thioanilides (**1**)

Compd	Yield (%)	m.p. (lit.)	Found (%) (Calc.)	
			C	H
1a	67	63-4 (62-4)[11]	—	—
1b	68	86-7 (85-87)[13]	—	—
1c	73	100-1 (97-99)[11]	—	—
1d	63	108-9	36.2 (36.3	2.8 2.7)
1e	57	128-30	32.4 (32.1	2.1 2.0)
1f	71	142-3	27.9 (28.0	1.8 1.8)
1g	75	161-2	25.7 (25.4	1.3 1.3)
1h	65	120-21	32.1 (32.1	2.0 2.0)
1i	75	145-46	25.0 (24.8	1.6 1.6)
1j	75	119-20	28.1 (28.0	1.8 1.8)
1k	78	166-7	30.2 (30.2	2.2 2.3)
1l	68	134-5	30.6 (30.2	2.4 2.3)
1m	70	164-5	26.9 (26.9	2.1 2.0)
1n	67	139-40	33.3 (33.5	2.8 2.8)
1o	77	132-3	43.4 (43.7	2.9 2.9)
1p	75	116-7 (114-6)[11]	—	—

pected benzothiazoles and/or the respective reduced (dehalogenated) products derived from the former, as secondary products. Thioanilides, in which both the *ortho*-positions were substituted with bromine (**1i, 1j, 1n**), on photolysis in methanol gave the corresponding 4-debrominated benzothiazoles (**2d, c, n'** respectively). Irradiation of the anilide **1i** afforded 4,6-dibromo-2-methylbenzothiazole (**2i**) which after isolation and further irradiation in methanol, furnished 6-bromo-2-methylbenzothiazole (**2d**). In the case of *p*-bromoanilides, irradiation in methanol yielded the 6-debrominated benzothiazoles if the anilide had also a substituent at either of the *meta*-positions. Thus, the thioanilides **1e, 1g, 1k** and **1l** on photolysis furnished the respective 6-unsubstituted benzothiazole (**2e, 2g', 2k'** and **2l**). It was also observed that the *p*-bromosubstituent in **1** was not normally replaced by hydrogen if there was no *meta*-substituent. Thus the photolysis of the anilides **1d** and **1o** gave the expected 6-bromobenzothiazoles (**2d** and **2o**). Similarly, irradiation of the tribromoanilide **1i** gave the normal benzothiazole (**2i**) and its reduced product both containing 6-bromo substituent.

In the above observations two exceptions were noticed. The irradiation of 2-chloro-4,6-dibromothioacetanilide (**1f**) in methanol afforded the reduced product, 4-chloro-2-methylbenzothiazole (**2f**) instead of 6-bromo-4-chloro-2-methylbenzothiazole. On the other hand, the anilide **1m** on irradiation furnished **2m** (**2m'**) without any indication of the expected reduction product 2,5- or 2,7-dimethylbenzothiazole. The characterization data of the photolysis products are given in Table 2.

The photolyses of *o*-halothioanilides (**1**) were also studied in benzene medium. It was observed that the cyclization to benzothiazoles takes place in almost the same efficiency as in methanol medium. A noteworthy difference noted was that arylation also occurred in the benzothiazole ring. When the substituent was bromine in the *para*-position of the thioanilide (e.g. **1f, 1o**) having no *meta*-substituent, the arylation took place giving the 6-phenylbenzothiazoles, **2f', 2f''** and **2o'**. However, when there was a substituent adjacent to the bromine (e.g. **1g, 1j, 1k, 1n**), no arylation took place resulting in the 4-bromo or 6-bromobenzothiazoles. However, 2,4,6-tribromothioacetanilide (**1i**) was found to be an exception which on irradiation in benzene furnished 4,6-dibromo-2-methylbenzothiazole (**2i**) in a high yield (82%).

The results of irradiation of the thioanilides (**1**) in methanol and benzene are given in Table 3. Two mechanisms could be considered for the formation of **2** from **1**. The first route may involve photoinduced cleavage of aryl-halogen bond with subsequent elimination of HX from the tautomeric enol form of the thiomide creating a diradical in the solvent cage, which could undergo cyclisation to give **2**. The second route may follow a benzyne mechanism involving the photoinduced elimination of HX followed by intramolecular cyclization by the addition of the enolic −SH group of the thioamide. The photolabile nature of the aryl-halogen bond is well known[2], the C-Br bond being weaker than C-Cl bond (C-Cl = 78 kcal/mol; C-Br = 66 kcal/mol)[3]. The enol nature of **1** was supported by the PMR signals in the region δ 2.2-2.5 due to SH proton. Compounds **1** showing sharp SH signals underwent cyclization to benzothiazoles in 12-15 hr, while those showing broad signals took 24-40 hr. The solvent cage mechanism appears to be operative since neither dehalogenated thioanilide nor a disulphide was detected.

Experimental Procedure

Melting points are uncorrected. IR spectra were recorded in KBr on a Beckmann IR-20 spectrophotometer, PMR spectra on Varian T-60 and Perkin-Elmer R-32 spectrometers (chemical shifts in δ, ppm) and mass spectra on Varian MAT-CH7 and MS-30 and Hitachi-Perkin Elmer RMU-6E instruments. irradiations were carried out in a Rayonet photochemical reactor model RPR-208 equipped with eight RUL-208 low pressure mercury lamps of wavelength 254 nm.

Bromoanilines

The required bromoanilines were prepared from the respective substituted anilines. Bromination was effected by the general procedure[4]. Following dibromoanilines were prepared: 2-bromo-4,6-dichloroaniline (m.p. 85°)[5], 4,6-dibromo-2-chloroaniline (m.p. 98°)[5], 2,6-dibromo-4-chloroaniline (m.p. 94-5°)[6], 2,4-dibromo-3-chloro-6-methylaniline (m.p. 79-80°), 4,6-dibromo-3-chloro-2-methylaniline (m.p. 76-77°), 4,6-dibromo-2,3-dichloroaniline (m.p. 104°), 2,6-dibromo-4-methylaniline (m.p. 81°)[7], 2,4-dibromo-6-phenylaniline (m.p. 53°)[8], 2,4,6-tribromo-3-methylaniline (m.p. 103°)[9], 2,4,6-tribromoaniline (m.p. 123-4°)[4]. All the bromoanilines were crystallized from aq. ethanol.

N-Arylacetamides

These were prepared from the above bromoanilines by the standard acetylation method[4] and crystallized from ethanol. In the case of 2-bromosubstituted anilines, acetylation was catalyzed by a few drops of conc. sulphuric acid. N-(4-Bromo-2-chlor-

Table 2—Characterization Data of Benzothiazoles (**2**)

Compd	m.p. lit.	Found (%) (Calc.) C	H	Spectral data
2a	151-152 (picrate) (153)[11]			PMR (CCl_4): 2.71 (*s*, 3H, CH_3), 6.93-8.0 (*m*, 4H, Ar-*H*)
2b	42-3 (38-9)[13]			PMR ($CDCl_3 + CCl_4$): 2.82 (*s*, 3H, CH_3), 7.2-8.0 (*m*, 3H, Ar-*H*)
2c	85-6 (84-6)[11]			PMR ($CDCl_3 + CCl_4$): 2.77 (*s*, 3H, CH_3), 7.3 (*dd*, 1H, C_5-H, J = 8 and 2 Hz), 7.75-7.9 (overlapping, 2H, C_4-H and C_7-H)
2d	88-9 (85-7)[12]			PMR ($CDCl_3 + CCl_4$): 2.8 (*s*, 3H, CH_3), 7.38-8.0 (*m*, 3H, Ar-*H*)
2f	50-51 (52-53)[14]			PMR ($CDCl_3 + CCl_4$): 2.83 (*s*, 3H, CH_3), 6.93-7.72 (*m*, 3H, Ar-*H*)
2g	181-2	32.4 (32.4	1.5 1.4)	PMR ($CDCl_3 + CCl_4$): 2.83 (*s*, 3H, CH_3), 7.93 (*s*, 1H, Ar-*H*)
2g′	130-1[15]			PMR ($CDCl_3 + CCl_4$): 2.87 (*s* 3H, CH_3), 7.3-7.6 (AB_q, 2H, J = 9 Hz) (expected C,H values were obtained) MS: *m/z* 217 (219, 221), M^+, 182 (184), 176, 180), 146, 141 (143)
2h	109-110 (105-7)[11]			PMR ($CDCl_3$): 2.83 (*s*, 3H, CH_3), 7.4-7.63 (2*d*, 2H, Ar-*H*, J = 2 Hz) MS: *m/z* 217 (219, 221), M^+, 182 (184), 176 (178, 180), 146, 141 (143), 106
2i	116-7	31.7 (31.3	1.8 1.6)	PMR (CCl_4): 2.87 (*s*, 3H, CH_3), 7.7 and 7.97 (2*d*, 2H, Ar-*H*, J = 2 Hz)
2j	116-7	37.1 (36.6	2.0 1.9)	PMR ($CDCl_2 + CCl_4$): 2.87 (*s*, 3H, CH_3), 7.62 and 7.74 (2*d*, 2H, Ar-*H*, J = 2 Hz)
2k	110-112	39.2 (39.1	2.5 2.6)	PMR (CCl_4): 2.77 (*s*, 6H, 2 CH_3), 7.81 (*s*, 1H, Ar-*H*) MS: *m/z* 275 (277, 279), M^+
2k′	100-101 (75)[16]			PMR ($CDCl_3 + CCl_4$): 2.75 and 2.8 (2*s*, two 3H, 2 CH_3), 7.22 and 7.52 (AB_q, 2H, Ar-*H*; J = 9 Hz) MS: *m/z* 197 (199), M^+, 182 (184), 162, 155 (157), 121
2l	88-9 (85)[16]			PMR (CCl_4): 2.60 and 2.76 (2*s*, two 3H, 2 CH_3), 6.98 and 7.14 (AB_q, 2H, Ar-*H*, J = 8 Hz) MS: *m/z* 197 (199), M^+, 196 (198), 182 (184), 162, 121
2m	150-2	33.7 (33.7	2.3 2.2)	PMR ($CDCl_3 + CCl_4$): 2.7 (*s*, 3H, CH_3), 2.84 (*s*, 3H, CH_3), 7.95 (*s*, 1H, Ar-*H*)
2n	(liquid)	44.5 (44.6	3.2 3.3)	PMR (CCl_4): 2.42 (*s*, 3H, C_6-CH_3), 2.81 (*s*, 3H, C_2-CH_3), 7.39 and 7.43 (*s*, 2H, Ar-*H*)
2n′	182-4 (picrate) (184-5)[11]			—
2o	94-6	55.1 (55.3	3.3 3.3)	PMR ($CDCl_3 + CCl_4$): 2.8 (*s*, 3H, CH_3), 7.3-8.0 (*m*, 7H, Ar-*H*)
2o′	129-131	79.6 (79.7	5.2 5.0)	PMR ($CDCl_3 + CCl_4$): 2.8 (*s*, 3H, CH_3), 7.2-8.0 (*m*, 12H, Ar-*H*)

ophenyl)acetamide and N-(4-bromo-2,3-dichlorophenyl)acetamide were prepared by bromination of the respective acetyl derivatives[10].

o-Halothioacetanilides (**1**): *General procedure*

The respective acetanilide (5.0 g) was treated with P_2S_5 (3-4 g) in dry benzene (150-200 ml) under reflux for 5-8 hr, monitoring the reaction by TLC. After the reaction was complete, the reaction mixture was cooled and the benzene solution separated by decantation. The residue was triturated twice with hot benzene and separated. The benzene extracts were combined and washed with water. The product was extracted twice or thrice with an ice-cold, 10% NaOH solution, till there was no thioamide in the benzene layer (TLC). The NaOH extract was

Table 3—Yields and Reaction Periods for the Formation of Benzothiazoles (**2**) from Irradiation of Thioacetanilides in Methanol and Benzene

Anilide	Irradiation in methanol			Irradiation in benzene		
	Product	Reaction period (hr)	Yield (%)	Product	Reaction period (hr)	Yield (%)
1a	**2a**	45	87	**2a**	44	77
1b	**2b**	42	64			
1c	**2c**	24	69			
1d	**2d**	24	62			
1e	**2e** (= **2b**)	24	59			
1f	**2f**	16	38	Inseparable mixture of **2f′** and **2f″**	22	40
1g	**2g′**	20	80	**2g**	12	77
1h	**2h**	15	74	**2h**	10	69
1i	**2i, 2d**	18	47, 23	**2i**	18	82
1j	**2j′** (= **2c**)	20	84	**2j**	12	91
1k	**2k′**	24	77	**2k**	24	78
1l	**2l**	18	61			
1m	**2m**	15	68			
1n	**2n′**	20	79	**2n**	15	56
1o	**2o**	24	59	**2o, 2o′**	35	35, 6
1p	**2p** (= **2h**)	17	94			

Irradiations in methanol were carried out with 1.0 g samples for **1a, c, e, f, j, n**; 1.5 g samples for **1b, d, h, i, o, p**; 2.0 g samples for **1g, k, l** and 3.5 g for **1m**. Irradiations in benzene were carried out with 1.0 g samples for **1a, f, i, j k**; 1.5 g of **1h**, 2.0 g of **1g**, 0.65 g of **1n**, and 1.7 g of **1o**.

acidified with dil. HCl (5%) or H_2SO_4 (5%) under cooling and the separated solid allowed to settle for 2-3 hr, filtered, dried, purified by column chromatography over silica gel using benzene-pet. ether (1:1) as eluant and crystallised from a mixture of benzene and pet. ether. The characterization data of **1** are given in Table 1.

Photolysis of **1** *in methanol*

In a typical run, N-(2,4-dichlorophenyl)thioacetamide (**1c**; 1.0 g) in methanol (150 ml) was irradiated (254 nm) for 24 hr in a quartz vessel and methanol distilled off. To the residue was added 5% NH_4OH solution (150 ml) and the mixture extracted with benzene. The benzene extract was dried, concentrated and passed through a basic alumina column (5 cm × 2 cm) to remove the polymeric material using benzene-pet. ether as eluant. The eluate was concentrated and chromatographed over a column of a silica gel to obtain 6-chloro-2-methylbenzothiazole (**2c**; 0.575 g, 69%) as a colourless solid, m.p. 85-6° (lit.[11], m.p. 84-6°) (benzene-pet. ether). The results obtained from the irradiation of other thioacetanilides are given in Table 3. The characterization data of the products are given in Table 2.

Photolysis of **1** *in benzene*

The reaction was carried out as in methanol. But, as the reaction began, the hydrobromide or hydrochloride of the resultant benzothiazole was deposited on the walls of the quartz vessel. The benzene solution was transferred to a flask and the solid deposits were dissolved in water, basified and extracted with benzene. The benzene extracts were combined, dried ($MgSO_4$), concentrated and purified as described above. The results are given in Table 3.

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Photoreactions of *trans*-Benzalacetone in Solution & Organised Media

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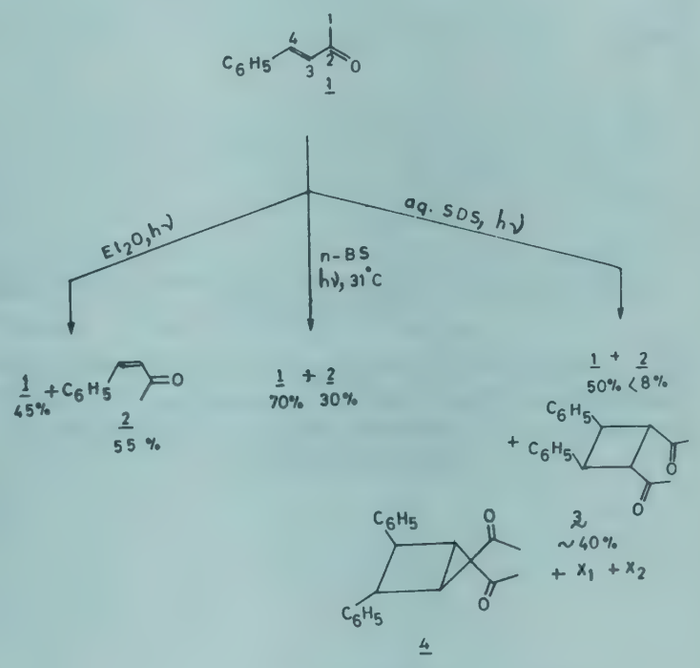
Direct photolysis of *trans*-benzalacetone (**1**) in diethyl ether results in the formation of a mixture of photoproducts containing *trans- and cis*-benzalacetones (**2**) in approximately 1:1 ratio. Irradiation of **1** in *n*-butyl stearate medium affords a photostationary state (PSS) mixture of **1** and **2** in 7:3 ratio. On the contrary, sodium dodecyl sulphate (SDS) micellized **1** primarily exhibits a bimolecular reaction with high selectivity affording the dimer **3** as major and **2** as minor products.

The study of photochemical reactions in organized media like micelles and luquid crystals has attracted much attention in recent years[1]. This is mainly because of their similarities to some biological systems[2] and ability to control the rate and stereochemical course of reactions. Herein we present our investigations on the photochemical behaviour of *trans*-benzalacetone (**1**) in diethyl ether, aq. sodium dodecyl sulphate (SDS) and *n*-butyl stearate (*n*-BS).

Photolysis of **1** in organic solvents has been reported to give *cis*-benzalacetone[3] (**2**) and a cyclic dimer[4]. Light-induced dimerization of solid **1** has been reported to afford the α-truxillic type dimer[5]. Recently, it has been reported[6] that the photo-dimerization of **1** in CTAB (a cationic micelle) and liquid crystalline solvent of cholesteryl system proceeded in a head-head fashion leading to *cis*-(**3**) as well as *trans*-(**4**) dimeric products. Some preference for *cis*-dimerization was also noted (Scheme 1).



SCHEME 1

The required *trans*-benzalacetone[7] (**1**) and *n*-butyl stearate (*n*-BS)[8] were prepared according to the procedures described in the literature, and characterized by their physical data (m.p., b.p., UV, IR and PMR). There was not much difference in the UV spectra of **1** in methanol (λ_{max} 288; ε, 17095), aq. SDS (λ_{max} 290; 18299) and *n*-BS (λ_{max} 285; ε, 17082).

Photolysis of **1** in ether primarily yielded the *cis*-benzalacetone (**2**) which was separated from **1** by HPLC (Fig. 1). The reaction plot for disappearance of **1** and appearance of **2** showed that a photostationary state (PSS) mixture containing 45% **1** and 55% **2** was obtained (Fig. 2). The formation of any dimeric product(s) was not observed under the conditions employed.

HPLC analysis (Fig. 3) of the photo-mixture obtained from the photolysis of **1** micellized in SDS

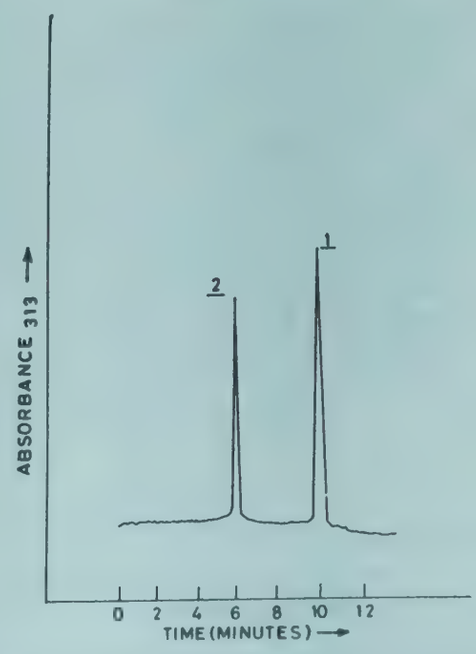


Fig. 1 – HPLC separation of *trans*-(**1**) and *cis*-benzalacetones (**2**).

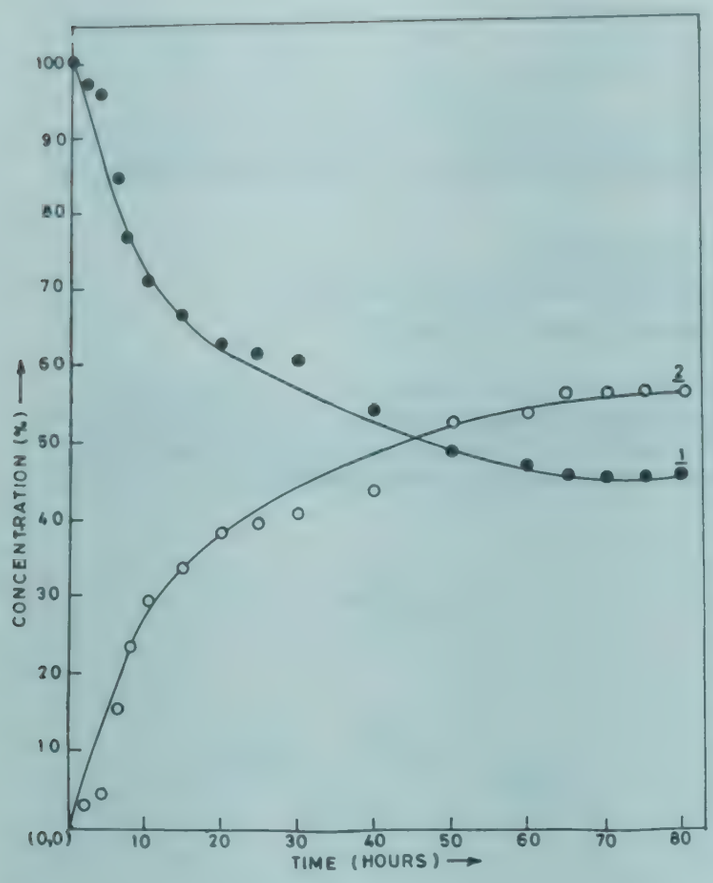


Fig. 2 – Reaction plots showing the conversion of *trans*-benzalacetone (**1**) with time into *cis*-benzalacetone (**2**) on direct irradiation of **1** in diethyl ether at 25°C. Photolysis was monitored by HPLC.

Fig. 3 – HPLC separation of photo-products of SDS-micellized *trans*-benzalacetone (**1**).

indicated the formation of a major product (~ 40%) with $R_t = 2$ min, and three minor products. The major product was isolated and characterized as *cis*-dimerization product **3** based on its characteristic spectral data and their comparison with those of other related compounds given in literature[5,11]. The IR spectrum of **3** exhibited a bifurcated peak for carbonyl group at 1720 and 1710 cm^{-1}. The splitting of carbonyl absorption band and its shift to higher frequency as compared to α-truxillic structure[5] (1696 cm^{-1} for α-truxillic C=O) can only be brought about by intercarbonylic electrostatic interactions[9,10]. The PMR spectrum revealed the presence of ten phenyl, six acetyl and four cyclobutyl protons. The appearance of a doublet for phenyl and a symmetrical multiplet for cyclobutyl protons supported the assigned structure **3** for the dimer. The compound with $R_t = 6$ min was identified as *cis*-benzalacetone (**2**) based on its R_t value and co-HPLC with an authentic sample of **2**. The other two products (X_1 and X_2) with $R_t = 5.3$ and 7.2 min present in ~5% could not be identified. The reaction plot shown in Fig. 4 indicates that **2** starts disappearing after getting accumulated upto ~10%. At the same time compound with $R_t = 7.2$ min starts ap-

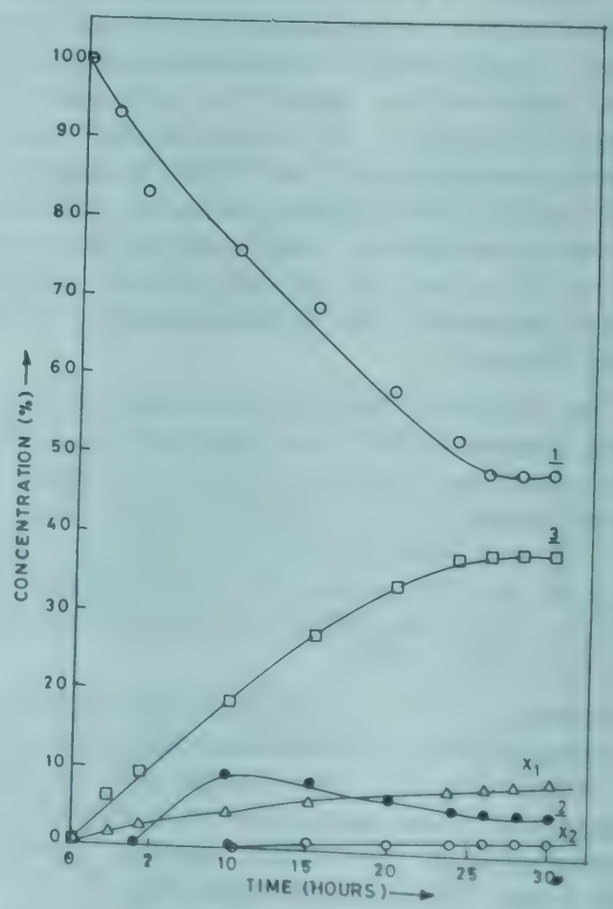


Fig. 4 – Reaction plots showing the photolytic conversion of aq. SDS-micellized *trans*-benzalacetone (**1**) with time into various products (3, 2, X_1 and X_2) at 25°C.

pearing. Therefore, the product is likely to be a dimer formed from either two *cis*- or one *cis*- and one *trans*-molecules of benzalacetone.

Photolysis of *trans*-benzalacetone (**1**) in *n*-BS at temperatures above 28° resulted in the formation of **2** only. The reaction plot indicated the presence of 30% of **2** in a PSS mixture. It is interesting to note that **1** undergoes *cis-trans* photoisomerization at 28° which is near the smectic phase (26.1°) of *n*-BS liquid crystal. Smectic structure is much more tightly ordered than cholesteric and nematic phases which are quite similar to isotropic media with regard to microscopic matrix effect determined by the short-range orientational order[12,13]. Formation of dimeric photo-products was not observed under the present photolytic conditions. Further, no photochemical reaction was observed at temperatures below 27°. It is known that the reactions conducted in liquid crystals are affected by the orderly arrangement of the crystals, viscosity of the medium orientation, concentration and chain length of the substrate. Viscosity of medium seems to play an important role in the present case by affecting the torsional potential curve of the excited benzalacetone. It is suggested[14] that the viscous flow solvent cage effect is added to influence the solute internal motions. Also, associated with the space requirements are the solvent induced barriers for rotations of magnitudes proportional to the number of solvent molecules to be displaced. Thus, there is a relatively large barrier for rotation of the double bond in benzalacetone in smectic and viscous isotropic *n*-BS as compared to the barrier present in solvents like diethyl ether.

Experimental Procedure

UV spectra were recorded in MeOH on a Beckman DU-6 spectrophotometer (λ_{max} in nm; logε in parentheses), IR spectra on a Perkin-Elmer 625 spectrophotometer (ν_{max} in cm^{-1}) and 60 MHz PMR spectra in $CDCl_3$ on a Hitachi-600 instrument using TMS as internal standard (chemical shifts in δ, ppm). HPLC analyses were performed on a Beckman 330 liquid chromatograph equipped with a Beckman model 165 wavelength selectable UV detector. The conditions of analyses were as follows: Altex Si-60 5μ, 150×4.5 mm, 5% EtOAc in pet. ether, 1 ml/min, 313 nm.

AR grade solvents, except pet. ether, were distilled before use. Technical pet. ether was purified and fractionated to collect fractions with b.p. 62-65°. *trans*-Benzalacetone (**1**)[7] and *n*-butyl stearate (*n*-BS)[8] were prepared and characterized according to the procedures given in literature. Sodium dodecyl sulphate (SDS) was obtained from Aldrich Chemical Company, Milwaukee, Wisconsin, USA and used as such. Evaporation of organic solvents was done under reduced pressure using Eyela rotary evaporator.

Photolysis samples were prepared by taking appropriate amounts of substrate and solvent in quartz vessels. These samples were then purged with nitrogen for 15 min, capped with a rubber septum and sealed with parafilm. Medium pressure 125 W Hg lamp housed in an Applied Photo-Physics Annular Photo-reactor model APQ 40, was used for irradiation. Percent isomeric compositions were determined from the area under the corrected HPLC peak.

Photolysis of trans-benzalacetone (**1**) *in diethyl ether*

A solution of **1** (0.50 g, 3.4 mmol) in dry ether (30 ml) was irradiated and the progress of reaction monitored by HPLC. Formation of a new peak with $R_t = 6$ min in addition to that of **1** with $R_t = 9.8$ min was observed. After 80 hr of photolysis, the new photo-product was isolated by flash column chromatography[15]. Evaporation of the solvent afforded 230 mg of *cis*-benzalacetone (**2**); UV: 285 (4.00), 220 (4.01); IR (neat): 3040, 2960, 2920, 2840, 1670, 1600, 1560, 1490, 1440, 1410, 1385, 1350, 1250, 1195, 1175, 1155, 1065, 1010, 965, 910, 825, 780-760, 740, 715, 680; PMR: 2.12 (3H, *s*, $-CO-CH_3$), 6.12 (1H, *d*, $J=12$ Hz, C_3-H), 6.88 (1H, *d*, $J=12$ Hz, C_4-H), 7.40 (5H, *m*, Ar−H).

Photolysis of SDS-micellized trans-benzalacetone (**1**)

trans-Benzalacetone (**1**; 0.20 g, 1.37 mmol) was micellized with SDS solution (25 ml, 10^{-2} *M* in distilled and deionized H_2O). The clear solution was irradiated and the progress of reaction followed by HPLC. The major photo-product with $R_t = 2$ min was isolated by flash chromatography and characterized as dimer **3**; IR ($CHCl_3$): 3030 (aromatic C−H), 2980, 2940 (aliphatic C−H), 1720 (C=O), 1615, 1510, 1465 (aromatic C=C), 1370 (δ_{C-H} of CH_3), 690, 709 (aromatic δ_{C-H}); PMR: 2.1 (6H, *s*, $-CO-CH_3$), 3.60-4.50 (4H, *m*, $4\times-CH$), 7.18 (10H, *d*, $2\times C_6H_5$).

Photolysis of **1** *in n-BS*

Mixtures of **1** (0.10 g, 0.68 mmol) and *n*-BS (10 ml) were taken in quartz tubes. After purging with the nitrogen in the isotropic phase at about 35°, each tube was capped and sealed. The tubes containing reaction mixtures were placed in the reactor and irradiated in the temperature range of

15 – 31°. The course of reaction in each case was monitored by HPLC. Photolysis at temperature above 28° resulted in the formation of *cis*-benzalacetone (**2**). Its presence was established by isolating it from the photolysis mixture after 65 hr and recording its physico-chemical properties.

Acknowledgement

The authors are thankful to the Department of Atomic Energy, Government of India for financial assistance.

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Synthesis of Oxa- & Thia- analogs of Bicyclo[n.3.0]alkanes

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A general and convenient synthetic approach for the formation of a variety of oxa- and thia- analogs of bicyclo[n.3.0]alkanes is described. This is illustrated by the synthesis of a series of 2-oxa(IIa-d)- and 2-thia(IIIa-d)- analogs of bicyclo[3.3.0]octane(I) on one hand and 4-oxa(Va-d)- and 4-thia(VIa-d)- analogs of bicyclo[5.3.0]decane(IV) on the other. The analogs of I and IV are obtained by cyclodehydration of the diols XIX and XXI respectively using dil. H_2SO_4 or DMSO. The diols in turn are prepared starting from the keto acids VII. On the otherhand, treatment of di-tosylates XX and XXII of XIX and XXI with Na_2S in refluxing ethanol affords the respective 2-thia(III)- and 4-thia(VI)- analogs of I and IV systems. The formation of oxolans(II) via oxidative cyclisation of the cycloalkaneethanols(XXIII) with lead tetraacetate is also described.

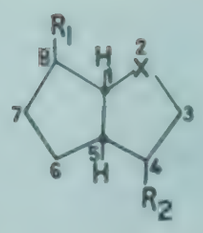
There has been a great deal of interest in the synthesis and reactions of cyclic ethers[1a-e] and heterocyclic compounds[1c] containing oxygen and sulphur but surprisingly only a few reports dealing with the chemistry of oxa- and thia- analogs of bicyclo[n.3.0]alkanes are available in the literature[2-4]. Cyclopentanoid monoterpenoids[5] such as nepetalactone, dihydronepetalactone, isodihydronepetalactone and iridoids, which contain an oxabicyclic or related lactone ring system, possess insecticidal, antihelminthic and antiseptic properties. Iridoids play a defensive role in insects. Therefore, our attention was drawn towards developing convenient routes for the synthesis of oxa- and thia- analogs of bicyclo[n.3.0]alkanes from simple starting materials. The syntheses of a variety of oxa(II/V)- and thia(III/VI)-analogs of *cis*-bicyclo[3.3.0]octane(*cis*-pentalane) (I) and *cis*-bicyclo[5.3.0]decane(IV), involving simple and convenient approaches and utilizing the same starting material are described in this paper.

Among the methods available for the construction of 5- to 7-membered oxygen heterocycles, cyclodehydration of diols is not only the most important and major route but also provides very simple synthesis of these systems. In addition to acid catalysts[6] such as H_2SO_4, H_3PO_4 and *p*-TsOH a relatively mild reagent such as DMSO[7,8] is found to be suitable in this procedure. Reagents like pyridinium chloride[9] and sulphonated polystyrene resins[10] are also very effective.

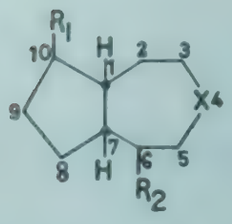
Two approaches were made in the present study: one involving cyclodehydration[6-8] of α, ω-diols and the other involving oxidative cyclisation[11-13] of cycloalkaneethanols. In the first approach besides the usual catalysts such as H_2SO_4, H_3PO_4, *p*-TsOH, DMSO was advantageously used to effect cyclisation of α,ω-diols giving the 2-oxa(IIa-d)- and 4-oxa(Va-d)- anlogs of I and IV respectively. The required diols were obtained starting from the keto acids VII.

To achieve the synthesis of fused oxolans(IIa-d), the keto acids(VIIa-d) were subjectd to lactonization in the presence of $NaBH_4$ to get the γ-lactones(XVIIa-d) which on reductive cleavage with LAH furnished the diols(XIXa-d) in good yields(72 to 88%). In an interesting observation, the lactones(XVIIa-d) on treatment with methanolic sodium methoxide underwent hydrolytic cleavage affording the hydroxymethyl esters(XVIIIa-d) in 49 to 55% yields. These esters (XVIIIa-d) on LAH reduction gave the diols(XIXa-d), identical in all respects with those obtained from the reductive cleavage of XVII. It should be mentioned here that these hydroxymethyl esters(XVIIIa-d) served as key intermediates in the synthesis of nepetalinic acids(XIV and XV)[14] — the degradation products of nepetalactone(XVI)[15], a major constituent and active principle of the oil of catmint (*Nepeta cataria*). In the present investigation, the diols(XIXa-d) were converted into the target bicyclic ethers(IIa-d) via cyclodehydration which was effected either with 18% H_2SO_4 or with DMSO. The yields in the latter case were better (Table 1).

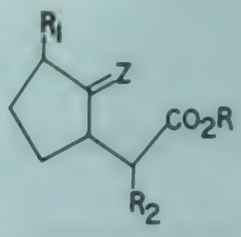
In the second approach the keto acids(VII) were subjected to the modified Wolff-Kishner reduction to give the acids(IXa-d) which were reduced to the corresponding cyclopentylethanols(XXIIIa-d) in 70 to 78% yields. As these alcohols(XXIIIa-d) have a δ-hydrogen[12,13], they could undergo oxidative cyclisation readily in the presence of LTA[12,13,16] in dry benzene to furnish the corresponding cyclic ethers(IIa-d). The oxida-

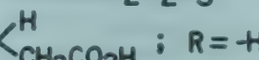
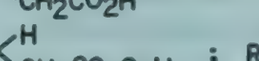


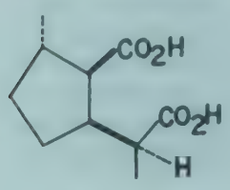
I X = CH_2 ; R_1=R_2=H
II X = O
III X = S



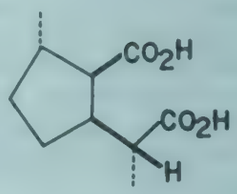
IV X = CH_2 ; R_1=R_2=H
V X = O
VI X = S



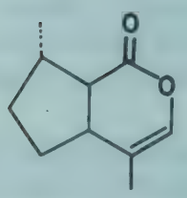
VII Z = O ; R = -H
VIII Z = O ; R = $-C_2H_5$
IX Z = H_2 ; R = -H
X Z = $C(CN)CO_2C_2H_5$; R = $-C_2H_5$
XI Z = ; R = $-C_2H_5$
XII Z =  ; R = -H
XIII Z =  ; R = $-C_2H_5$



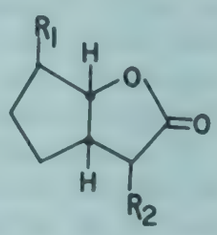
XIV



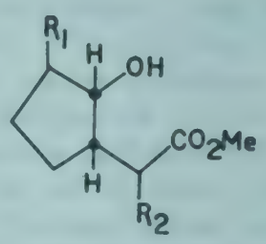
XV



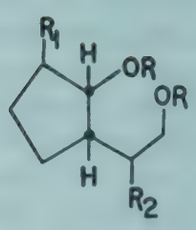
XVI



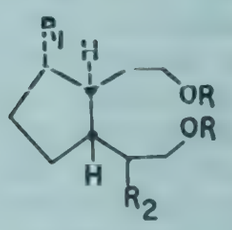
XVII



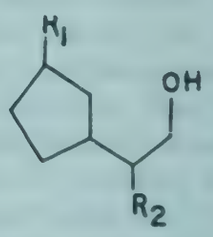
XVIII



XIX R = H
XX R = Ts



XXI R = H
XXII R = Ts



XXIII

a. R_1 = R_2 = H
b. R_1 = CH_3 ; R_2 = H
c. R_1 = H ; R_2 = CH_3
d. R_1 = R_2 = CH_3

tive cyclisation of XXIIIa-d was infact found to be advantageous to get the corresponding oxolans(IIa-d) in yields ranging from 89 to 93%. Although the precise mechanism[17] of oxidative cyclisation may vary with the structure of the alcohol and the reaction conditions, a generally accepted common feature is the intramolecular 1,5-abstraction of a δ-hydrogen atom by an alkoxy radical formed by homolysis of the alkoxylated triacetate.

The oxidative cyclisation of cycloalkaneethanols(XXIIIa-d) using LTA was not only found to be a superior method leading to better yields of oxolans(IIa-d) in comparison to those of cyclodehydration method but also provided an interesting example of the intramolecular radical reaction. The yields of IIa-d by different methods are given in Table 1.

The keto acids VII were also elaborated to the oxepans(Va-d). The ethyl esters(VIIIa-d) of VII when subjected to Cope condensation gave the alkylidene cyanoesters(Xa-d) which were reduced to the saturated nitriles(XIa-d) with $NaBH_4$ in etha-

Table 1—Percentage Yields of IIa-d Obtained by (i) Cyclodehydration and (ii) Oxidative Cyclisation Methods

Compd	Yield (%)		
	(i) Cyclodehydration		(ii) LTA
	H_2SO_4	DMSO	
IIa	50	65	93
IIb	56	65	89
IIc	55	66	90
IId	54	64	89

nol. The nitriles(XIa-d) on decarboxlative hydrolysis afforded the desired diacids(XIIa-d), the diethyl esters(XIIIa-d) of which were reduced with LAH in boiling THF to furnish the bis-hydroxyethyl compounds(XXIa-d) in 55 to 60% yields. Cyclodehydration of these α,ω-diols(XXIa-d) either with 18% H_2SO_4 or DMSO provided the desired oxepans(Va-d) in 30 to 35% and 50 to 55% yields respectively.

The diols XIXa-d and XXIa-d were also converted into the 2-thia-*cis*-bicyclo[3.3.0]octanes (IIIa-d) and 4-thia-*cis*-bicyclo[5.3.0]decanes (VIa-d) respectively by treatment of their di-tosylates XXa-d and XXIIa-d with sodium sulphide nonhydrate ($Na_2S.9H_2O$) in refluxing ethanol.

The 2-oxa(IIa-d)- and 4-oxa(Va-d)- analogs of I and IV had a characteristic camphor like odour while the corresponding 2-thia(IIIa-d)- and 4-thia(VIa-d)- analogs had a strong characteristic but penetrating odour. The IR spectra of the fused oxolans(IIa-d) and oxepans(Va-d) as well as the thia- analogs (IIIa-d and VIa-d) distinctly showed the absence of >C=O and -OH groups and the presence of -C-O-C-(1050-1300 cm^{-1}) and -C-S-C-(1400-1500 cm^{-1}) linkages. Further, the oxa- and thia- analogs were also characterised by their PMR spectral data.

Experimental Procedure

All b.ps and m.ps are uncorrected. IR specra in KBr were recorded on a Beckman-Aculab 10 spectrophotometer (ν_{max} in cm^{-1}), and 60 MHz PMR spectra in CCl_4 on a Perkin-Hitachi R-24 spectrophotometer using TMS as internal standard(chemical shifts in δ, ppm). Homogeneity of the compounds was tested by TLC on plates coated with silica gel G(Stahl type 60) using iodine vapours for visualizing the spots.

2-Oxocyclopentane-1-alkanoic acids(VII)

The keto acids VIIa and VIIb were prepared from ethyl 2-oxocyclopentane-1-carboxylate and ethyl 3-methyl-2-oxocyclopentane-1-carboxylate respectively by alkylating with ethyl chloroacetate followed by decarboxylative hydrolysis whereas alkylation of the respective foregoing cyclopentanone esters with ethyl α-bromopropionate and subsequent decarboxylative hydrolysis provided the acids VIIc and VIId following the procedure reported earlier from this laboratory[18b,c]. The acids(VIIa-d) were purified by distillation under reduced pressure, and converted into esters(VIIIa-d) by EtOH-HCl method. The characterization data of VIIa-d and VIIIa-d are given below:

VIIa: Yield 60%, b.p. 98-100°/10mm, m.p. 48° (pet. ether 60-80°); IR: 2980, 1740, 1400, 1160; 2,4-DNPH derivative: m.p. 137°(EtOH); VIIIa[3b,18a-c]; yield 65%, b.p. 107-10°/10mm; IR: 2960, 1750, 1450.

VIIb: Yield 58%, b.p. 112°/10mm; 2,4-DNPH derivative: m.p. 130°(EtOH); VIIIb: yield 50%, b.p. 108-10°/10mm.

VIIc: Yield 65%, b.p. 110-12°/10mm; 2,4-DNPH derivative: m.p. 90°(EtOH); VIIIc: yield 52%, b.p. 115-18°/10mm.

VIId: Yield 62%, b.p. 114-15°/10mm; 2,4-DNPH derivative: m.p. 107°(EtOH); VIIId: yield 50%, b.p. 118-20°/10mm.

Reductive lactonization of keto acids(VII): Formation of 2-oxa-cis-bicyclo[3.3.0]octan-3-ones(XVII): General procedure

The keto acids(VIIa-d) were converted into the corresponding γ-lactones(XVIIa-d) following the procedure of Dixon *et al.*[19]. Their characterization data are given below:

XVIIa[3b]: Yield 63%, b.p. 108-10°/10mm; IR: 2980, 1780, 1440, 1360, 1190, 1150, 1040, 1000 (Found: C, 66.4; H, 7.7. $C_7H_{10}O_2$ requires C,66.6; H, 7.9%).

XVIIb: Yield 62%, b.p. 114-15°/10mm (Found: C, 68.2; H, 8.3. $C_8H_{12}O_2$ requires C, 68.6; H, 8.5%).

XVIIc: Yield 57%, b.p. 110-12°/10mm (Found: C, 68.3; H, 8.3. $C_8H_{12}O_2$ requires C, 68.6; H, 8.5%).

XVIId: Yield 55%, b.p. 110-15°/10mm (Found: C, 69.7; H, 8.9. $C_9H_{14}O_2$ requires C, 70.1; H, 9.0%).

Hydrolytic cleavage of XVIIa-d: Formation of methyl 2-hydroxycyclopentane-1-alkanoates(XVIII): General procedure[19]

The lactone(XVII) (0.01mol) was dissolved in dry methanol(16ml) and reacted with freshly prepared sodium methoxide(2g). After the reaction mixture was stirred at 20° for 90hr, it was acidifi-

ed with gl. acetic acid(2ml), and most of methanol removed under reduced pressure. Water was then added and the product isolated by continuous extraction with ether. The combined ether layer was washed successively with 10% Na_2CO_3 solution and brine, dried($MgSO_4$), solvent removed and the alcohol ester(XVIII) obtained as a thick oil. The following hydroxy esters were prepared:

XVIIIa: Yield 55%; IR: 3400, 2960, 2870, 1630, 1050 (Found: C, 60.1; H, 8.5. $C_8H_{14}O_3$ requires C, 60.7; H, 8.9%).

XVIIIb: Yield 52% (Found: C, 61.9; H, 9.2. $C_9H_{16}O_3$ requires C, 62.8; H, 9.9%).

XVIIIc: Yield 54% (Found: C, 62.1; H, 9.4. $C_9H_{16}O_3$ requires C, 62.8; H, 9.9%).

XVIIId: Yield 49% (Found: C, 63.9; H, 9.2. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%).

cis-β-(2-*Hydroxycyclopentyl*)*alkanols*(*XIX*): *General procedure*

Following the method of Clive and Kale[20], the foregoing lactones(XVIIa-d) were subjected to reductive cleavage to provide the diols(XIXa-d). The crude diols(XIX) are purified by passing through a column of neutral alumina using dry benzene as eluant. Their characterization data are given below:

XIXa[3b]: Yield 80%; IR: 3400-3300, 2980, 1120, 1040, 1025 (Found: C, 64,1; H, 10.5. $C_7H_{14}O_2$ requires C, 64.6; H, 10.7%); 3,5-DNP derivative: m.p. 87°(EtOH).

XIXb: Yield 72% (Found: C, 66.2; H, 10.8. $C_8H_{16}O_2$ requires C, 66.6; H, 11.1%); 3,5-DNP derivative: m.p. 94-95°(EtOH).

XIXc: Yield 88% (Found: C, 66.2; H, 10.8. $C_8H_{16}O_2$ requires C, 66.6; H, 11.1%); 3,5-DNP derivative: m.p. 107°(EtOH).

XIXd: Yield 78% (Found: C, 68.0; H, 11.0. $C_9H_{18}O_2$ requires C, 68.4; H, 11.4%); 3,5-DNP derivative: m.p. 114-15°(EtOH).

cis-Cyclopentane-1,1-*dialkanoic acids*(*XII*)

These acids were prepared in the following steps:

(a) The unsaturated cyanoesters(Xa-d) were prepared from the corresponding keto esters(VIIIa-d) by the general procedure of Cope *et al.*[21] and were obtained as thick colourless liquids. The following unsaturated esters were prepared: Xa[18a-c]: Yield 65%, b.p. 190-200°/10mm; Xb: yield 60%, b.p. 185-90°/10mm; Xc: yield 66%, b.p. 170-75°/10mm; Xd: yield 63%, b.p. 165-70°/10mm.

(b) The foregoing αβ-unsaturated cyanoesters(Xa-d) were reduced to the corresponding saturated cyanoesters(XIa-d) by $NaBH_4$ in molar ratios[22]. A solution of X(0.07mol) in ethanol(40ml) was added dropwise over a period of 1hr to a stirred solution of $NaBH_4$(1.2g) in ethanol(80ml) at 0°. After an additional stirring for 2hr at 20°, the mixture was poured into saturated brine and the product isolated by repeated extraction with benzene. The benzene extracts were dried($MgSO_4$) and the solvent was removed. The residue on distillation under reduced pressure afforded the following cyanoesters:

XIa: Yield 70%, b.p. 145-50°/10mm (Found: C, 62.7; H, 7.6; N, 5.0. $C_{14}H_{21}O_4N$ requires C, 62.9; H, 7.9; N, 5.2%).

XIb: Yield 69%, b.p. 138-45°/10mm (Found: C, 63.7; H. 7.7; N, 4.8. $C_{15}H_{23}O_4N$ requires C, 64.0; H, 8.1; N, 5.0%).

XIc: Yield 72%, b.p. 140-45°/10mm (Found: C, 63.8; H, 7.9; N, 4.7. $C_{15}H_{23}O_4$ N requires C, 64.0; H, 8.1; N, 5.0%).

XId: Yield 65%, b.p. 130-35°/10mm (Found: C, 64.8; H, 8.3; N, 4.6. $C_{16}H_{25}O_4N$ requires C, 65.0; H, 8.5; N, 4.7%).

(c) The above cyanoesters(XIa-d) were subjected to decarboxylative hydrolysis to provide the diacids(XIIa-d). In a typical procedure the cyanoester(XI) (0.07mol) was refluxed with conc. HCl(60ml) and gl. acetic acid(90ml) for 15hr. The reaction mixture was made free of excess acids(HCl and AcOH). The resulting crude diacid(XII) was repeatedly extracted with ether and the combined ether extracts were dried(Na_2SO_4). Removal of solvent gave XII which was purified by dissolving in 5% $NaHCO_3$ followed by treatment with charcoal and acidification. The corresponding ethyl esters(XIIIa-d) were prepared by azeotropic esterification method using benzene as solvent. The characterization data of the diacids(XIIa-d) and their esters(XIIIa-d) are given below:

XIIa[18b,c]: Yield 40%, m.p. 172° (Found: C, 59.7; H, 6.9, $C_9H_{14}O_4$ requires C, 59.9; H, 7.1%); XIIIa: yield 70%, b.p. 135-40°/10mm (Found: C, 64.9; H, 8.8. $C_{13}H_{22}O_4$ requires C, 65.0; H, 8.6%).

XIIb: Yield 45%, m.p. 123-24° (Found: C, 59.6; H, 7.8. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.0%); XIIIb: yield 65%, b.p. 128-32°/10 mm (Found: C, 65.7; H, 8.5. $C_{14}H_{24}O_4$ requires C, 66.0; H, 8.8).

XIIc: Yield 43%, m.p. 108-10° (Found: C, 60.2; H, 6.8. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.0%); XIIIc: yield 68%, b.p. 145-50°/10mm (Found: C, 65.8; H, 8.5. $C_{14}H_{24}O_4$ requires C, 66.0; H, 8.8%).

XIId: Yield 44%, m.p. 117-19° (Found: C, 61.4; H, 8.1. $C_{11}H_{18}O_4$ requires C, 61.7; H, 8.4%); XIIId:

yield 74%, b.p. 140-45°/10 mm (Found: C, 66.3; H, 9.7. $C_{15}H_{26}O_4$ requires C, 66.7; H, 9.6%).

LAH reduction of diacids(XIIa-d): Formation of diols(XXIa-d): General procedure

To a stirred suspension of LAH(3.9g) in dry ether(225ml), a solution of diacid(XII) (0.05mol) in dry ether(115ml) was added dropwise during 45min at 0°. Stirring was continued for another 1hr, and ice-water and H_2SO_4(10%) were added cautiously. The reaction mixture was left overnight, and the ether layer separated, washed well with brine, dried($MgSO_4$), and solvent removed. The residual oil was distilled under pressure to give XXI. The characterization data of the diols(XXIa-d) are given below:

XXIa: Yield 58%, b.p. 120-25°/10mm; IR: 3420, 2980, 2865, 1440, 1020 (Found: C, 68.0; H, 11.1. $C_9H_{18}O_2$ requires C, 68.4; H, 11.4%); di-tosyl derivative: m.p. 111-12°.

XXIb: Yield 60%, b.p. 112-15°/10mm (Found: C, 69.5; H, 11.4. $C_{10}H_{20}O_2$ requires C, 69.8; H, 11.6%); di-tosyl derivative: m.p. 118°.

XXIc: Yield 55%, b.p. 105-108°/10mm (Found: C, 69.4; H, 11.3. $C_{10}H_{20}O_2$ requires C, 69.8; H, 11.6%); di-tosyl derivative: m.p. 113-14°.

XXId: Yield 56%, b.p. 110-12°/10mm (Found: C, 70.8; H, 11.6. $C_{11}H_{22}O_2$ requires C, 71.0; H, 11.8%); di-tosyl derivative: m.p. 120°.

Cyclodehydration of diols(XIXa-d and XXIa-d): Formation of 2-oxa-cis-bicyclo[3.3.0]octanes(IIa-d) and 4-oxa-cis-bicyclo[5.3.0]decanes(Va-d): General procedure

Method-1 (using sulphuric acid)

A mixture of XIX or XXI (0.025mol) and H_2SO_4(20ml; 18%) was heated under reflux for 20min. Thereafter, the mixture was distilled till no more oil passed while taking care to maintain the volume of liquid in the distillation flask by gradually adding water during distillation. The distillate was extracted with ether and the organic phase dried(K_2CO_3). Solvent was removed and the crude product purified by passing through a column of alumina using benzene-pet. ether (1:1) as eluant. The oxolans(IIa-d) were obtained in 50 to 56% yields while the oxepans(Va-d) were obtained in 30 to 35% yields as colourless oily liquids having a characteristic camphor like odour.

Method-2 (using DMSO)[8]

A mixture of XIX or XXI(0.051mol) and DMSO)48g; 0.615mol) was heated under reflux at 156-68° for 13hr, cooled, treated with water(150ml), and extracted twice with pet. ether(2 × 100ml). The organic phase was dried($CaSO_4$), solvent removed and the product purified as described in method-1 providing the TLC-pure cyclic ether II or V in 64 to 66% and 50 to 55% yields respectively. These oxa- compounds were colourless liquids having penetrating and camphor like odour. The characterization data of IIa-d and Va-d are given below:

IIa: b.p. 142-43°; n_D^{24} 1.4575; IR: 2880, 2820, 2770, 1440, 1350, 1200, 1100, 1080, 1050, 920; PMR: 1.15-2.3(*m*, 9H), 3.85-4.3(*m*, 3H, CH_2-O-CH) (Found: C, 74.7; H, 10.5. $C_7H_{12}O$ requires C, 75.0; H, 10.7%).

IIb: b.p. 145-46°; n_D^{24} 1.4582; PMR: 1.11(*d*, 3H, CH_3 at C-8), 1.12-2.3(*m*, 8H), 3.85-4.2(*m*, 3H, CH_2-O-CH) (Found: C, 76.0, H, 10.8. $C_8H_{14}O$ requires C, 76.2; H, 11.1%).

IIc: b.p. 144-45°; n_D^{24} 1.4578; PMR: 1.15(*d*, 3H, CH_3 at C-4), 1.2-2.25(*m*, 8H), 3.80-4.4(*m*, 3H, CH_2-O-CH) (Found: C, 75.9; H, 10.8. $C_8H_{14}O$ requires C, 76.2; H, 11.1%).

IId: b.p. 147-48°; n_D^{24} 1.4580; PMR: 1.10(*d*, 3H, CH_3 at C-4), 1.12(*d*, 3H, CH_3 at C-8), 1.2-2.12(*m*, 7H), 3.75-4.25(*m*, 3H, CH_2-O-CH) (Found: C, 76.8; H, 11.2. $C_9H_{16}O$ requires C, 77.1; H, 11.4%).

Va: b.p. 165-66°; n_D^{24} 1.5720; IR: 2840, 2810, 1450, 1335, 1220, 1160, 1080, 1030, 975, 820; PMR: 1.1-2.5(*m*, 12H), 3.62(*m*, 4H, CH_2-O-CH_2) (Found: C, 78.2; H, 11.2. $C_9H_{16}O$ requires C, 77.1; H, 11.4%).

Vb: b.p. 168-69°; n_D^{24} 1.5732; PMR: 1.12(*d*, 3H, CH_3 at C-10), 1.25-2.35(br, *m*, 11H), 3.65(*m*, 4H, CH_2-O-CH_2) (Found: C, 78.3; H, 11.6. $C_{10}H_{18}O$ requires C, 77.9; H, 11.7%).

Vc: b.p. 170-72°; n_D^{24} 1.5705; PMR: 1.1(*d*, 3H, CH_3 at C-6), 1.15-2.24(*m*, 11H), 3.7(*m*, 4H, CH_2-O-CH_2) (Found: C, 78.2; H, 11.5. $C_{10}H_{18}O$ requires C,77.9; H, 11.7%).

Vd: b.p. 170-75°; n_D^{24} 1.5735; PMR: 1.12(*d*, 3H, CH_3 at C-6), 1.15(*d*, 3H, CH_3 at C-10), 1.2-2.3 (br, *m*, 10H), 3.65 (*m*, 4H, CH_2-O-CH_2) (Found: C, 79.0; H, 12.3, $C_{11}H_{20}O$ requires C, 78.6; H, 11.9%).

Wolff-Kishner reduction of VIIa-d: Formation of cyclopentane-1-alkanoic acids(IX): General procedure

The keto acid(VII) (0.1mol) was mixed with KOH(10g), ethylene glycol(80ml) and hydrazine hydrate(8ml; 98%). The mixture was refluxed using a Dean-Stark apparatus at 160-65° until no more water collected. The temperature was then raised to 195-200° and refluxing continued for

4hr. On cooling, the reaction mixture was treated with ice-water, acidified with HCl, and extracted with ether, and the ether extract washed with brine and dried ($MgSO_4$). Removal of solvent left the crude acid(IX) which was purified by distillation under reduced pressure, yield 75 to 80%. The characterization data of the acids thus prepared are given below:

IXa: b.p. 114-16°/10mm (lit.[23a-e] b.p. 117-18°/12mm); anilide derivative: m.p. 74°(EtOH) (Found: C, 76.6; H, 8.0; N, 6.6. $C_{13}H_{17}NO$ requires C, 76.8; H, 8.3; N, 6.8%).

IXb: b.p. 120-22°/10mm; anilide derivative: m.p. 83°(EtOH) (Found: C, 77.5; H, 8.4; N, 6.2. $C_{14}H_{19}NO$ requires C, 77.8; H, 8.7; N, 6.4%).

IXc: b.p. 115-17°/10mm, m.p. 139-40° (lit.[24] m.p. 140.5-144°); anilide derivative: m.p. 92°(EtOH) (Found: C, 77.6; H, 8.4; N, 6.2. $C_{14}H_{19}NO$ requires C, 77.8; H, 8.7; N, 6.4%).

IXd: b.p. 128-30°/10mm; anilide derivative: m.p. 105°(EtOH) (Found: C, 76.9; H, 8.8; N, 5.7. $C_{15}H_{21}NO$ requires C, 77.2; H, 9.0; N, 6.0%).

LAH reduction of IXa-d: Formation of cyclopentan-1-alkanols(XXIIIa-d): General procedure

The acid IX(0.02mol) in dry THF(100ml) was added to a stirred suspension of LAH(1.7g) in dry THF(100ml) at 90° during 1hr. The mixture was refluxed for another 3hr, cooled in ice-bath, and waer(2ml) added to it. Thereafter aq. NaOH(10%; 2.5ml) and water(2ml) were added successively, and the reaction mixture was filtered, THF evaporated under reduced pressure and the product taken up in ether. The ethereal solution was washed successively with $NaHCO_3$(10%) and brine, dried ($MgSO_4$) and solvent removed. The residue on purification by distillation under reduced pressure gave XXIII. Following alcohols(XXIIIa-d) were prepared:

XXIIIa: Yield 78%, b.p. 88-90°/20mm (lit.[23c,d] b.p. 97°/24mm); IR: 3350, 2900, 1120, 1050, 1040, 990 (Found: C, 73.3; H, 12.4. $C_7H_{14}O$ requires C, 73.6; H, 12.7%); 3,5-DNB derivative: m.p. 60°(EtOH).

XXIIIb: Yield 75%, b.p. 80-85°/20mm (Found: C, 74.6; H, 12.2. $C_8H_{16}O$ requires C, 75.0; H, 12.5%); 3,5-DNB derivatives: m.p. 65°(EtOH).

XXIIIc: Yield 70%, b.p. 82-84°/20mm (Found: C, 74.6; H, 12.2. $C_8H_{16}O$ requires C, 75.0; H, 12.5%); 3,5-DNB derivative: m.p. 63-64°(EtOH).

XXIIId: Yield 72%, b.p. 78-79°/20mm (Found: C, 75.7; H, 12.4. Calc. for $C_9H_{18}O$: C, 76.0; H, 12.6%); 3,5-DNB derivativse: m.p. 70°(EtOH).

Oxidative cyclisation of XXIIIa-d using LTA: Formation of IIa-d: General procedure

A stirred mixture of dry benzene(200ml), LTA(35.5g; 0.08mol) and anhyd. $CaCO_3$(15g) was heated under reflux. The alcohol(XXIII) (0.078mol) in dry benzene(50ml) was added in one batch, and the mixture refluxed for 48hr, cooled, filtered, water(25ml) added to the filtrate and the solution stirred(30min) to hydrolyse any unreacted LTA. The mixture was filtered under suction giving a clear two phase filtrate. The aqueous layer was removed and the benzene layer once washed with brine and dried(Na_2SO_4). Removal of the solvent gave the crude oxa-compound(II) which was purified by column chromatography over neutral alumina. Elution with benzene-pet. ether(1:1) followed by distillation gave II(89-93%). Compounds IIa-d, thus prepared, were identical (b.p., co-TLC, IR, PMR) with those obtained from cyclodehydration of the diols (XIXa-d).

2-Thia-cis-bicyclo[3.3.0]octanes(IIIa-d) and 4-thia-cis-bicyclo[5.3.0]decanes(VIa-d)

Conversion of the diols(XIXa-d and XXIa-d) into the corresponding di-tosylates(XXa-d and XXIIa-d) was carried by the folloing general procedure[26]:

A solution of XIX or XXI(0.005mol) in dry pyridine(5ml) was mixed with *p*-TsCl(1.36g) at 0-5°. After stirring for 2hr at this temperature and keeping overnight at room temperature, the solution was poured into ice and stirred well with conc. HCl(50ml) and extracted with ether. The ether phase was washed successively with 2*N* HCl, saturated $NaHCO_3$ and brine, dried($MgSO_4$) and solvent removed to give the crude tosylates(XIXa-d) and (XXIa-d) in 65 to 67% and 60 to 65% yields respectively as pleasant smelling compounds which were directly used in the next operation as per the following procedure[27].

A solution of XX or XXII(0.0012mol) and $Na_2S.9H_2O$(0.92g) in ethanol(5ml) and water(5ml) was heated under reflux for 12hr, ethanol removed under reduced pressure and the residue extracted with dichloromethane(3 × 75ml). Drying($MgSO_4$) and evaporation of the solvent gave the *cis*-thia- compound III or VI in 44 to 52% and 45 to 50% yields respectively as a colourless oil having characteristic but penetrating odour. Final purification of the thia- derivative was effected by column chromatography followed by distillation. The following thia- compounds were prepared:

IIIa: Yield 50%, b.p. 82°/20mm; n_D^{24} 1.5237; IR: 2980, 2870, 1600, 1470, 1450, 1410, 1380,

1250, 1200, 1135, 1090, 1030, 870, 730; PMR: 1.2-2.25(br *m*, 9H), 2.71-3.9(*m*, 3H, CH_2-S-CH) (Found: C, 65.3; H, 9.1. $C_7H_{12}S$ requires C, 65.6; H, 9.4%).

IIIb: Yield 44%, b.p. 78-80°/20mm; n_D^{24} 1.5239; PMR: 1.1(*d*, 3H, CH_3 at C-8), 1.15-2.3(br *m*, 8H), 2.88-3.90(*m*, 3H, CH_2-S-CH) (Found: C, 67.4; H, 9.5. $C_8H_{14}S$ requires C, 67.6; H, 9.8%).

IIIc: Yield 52%, b.p. 85°/20mm; n_D^{24} 1.5240; PMR: 1.12(*d*, 3H, CH_3 at C-4), 1.2-2.25(br, *m*, 8H), 2.75-4.01(*m*, 3H, CH_2-S-CH) (Found: C, 67.4; H, 9.4. $C_8H_{14}S$ requires C, 67.6; H, 9.8%).

IIId: Yield 46%, b.p. 75-76°/20mm; n_D^{24} 1.5241; PMR: 1.1(*d*, 3H, CH_3 at C-4), 1.13(*d*, 3H, CH_3 at C-8), 1.21-2.2(br *m*, 7H), 2.75-3.9(*m*, 3H, CH_2-S-CH) (Found: C, 68.9; H, 9.9. $C_9H_{16}S$ requires C, 69.2; H, 10.2%).

VIa: Yield 45%, b.p. 120-22°/20mm; n_D^{24} 1.5420; PMR: 1.15-2.3(br *m*, 12H), 2.71(*m*, 4H, CH_2-S-CH_2) (Found: C, 69.4; H, 10.0. $C_9H_{16}S$ requires C, 69.2; H, 10.2%).

VIb: Yield 48%, b.p. 114-15°/20mm; n_D^{24} 1.5310; PMR: 1.05(*d*, 3H, CH_3 at C-10), 1.15-2.35(br *m*, 11H), 2.72(*m*, 4H, CH_2-S-CH_2) (Found: C, 70.4; H, 10.2. $C_{10}H_{18}S$ requires C, 70.6; H, 10.6%).

VIc: Yield 50%, b.p. 112°/20mm; n_D^{24} 1.5330; PMR: 1.1(*d*, 3H, CH_3 at C-6), 1.15-2.24(*m*, 11H), 2.75(*m*, 4H, CH_2-S-CH_2) (Found: C, 70.4; H, 10.5. $C_{10}H_{18}S$ requires C, 70.6; H, 10.6%).

VId: Yield 45%, b.p. 123°/20mm; n_D^{24} 1.5354; PMR: 1.05(*d*, 3H, CH_3 at C-6), 1.1(*d*, 3H, CH_3 at C-10), 1.2-2.3(br *m*, 10H), 2.7(*m*, 4H, CH_2-S-CH_2) (Found: C, 71.4; H, 10.7. $C_{11}H_{20}S$ requires C, 71.7; H, 10.9%).

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Syntheses of 1,5-Benzothiazepines: Part II—Synthesis of 4-Aryl-2-carboxy-2, 3-dihydro-1, 5-benzothiazepines

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β-Aroylacrylic acids (II) react with 2-aminothiophenols(I) in ethanol containing gl. acetic acid to give 4-aryl-2-carboxy-2, 3-dihydro-1, 5-benzothiazepines(VII). Their structures have been established by elemental analyses and spectral data (IR, PMR, ^{13}C NMR and mass).

The successful therapeutic utilization of 1,5-benzothiazepine class of compounds such as diltiazem[1], thiazesim[2], etc. prompted us to synthesize new compounds of this class as potential pharmacological agents. Since the reactions of 2-aminothiophenol with α, β-unsaturated acids[3] and α, β-unsaturated carbonyl compounds[4] are reported to give 1, 5-benzothiazepines, we studied the reactions of 2-aminothiophenols with α, β-unsaturated keto acids. In our earlier study[5], we used methanol-gl, acetic acid, toluene or xylene as solvent for obtaining 1,5-benzothiazepine derivatives from the reaction of 2-aminothiophenol with chalkones. We have also used[6,7] xylene, ethanol and pyridine in similar reactions. In this paper the reactions of 2-aminothiophenol (Ia) and 2-amino-5-methylthiophenol (Ib)[8] with β-aroylacrylic acids (II)[9] under Thiele and Steimmig[10] conditions are described.

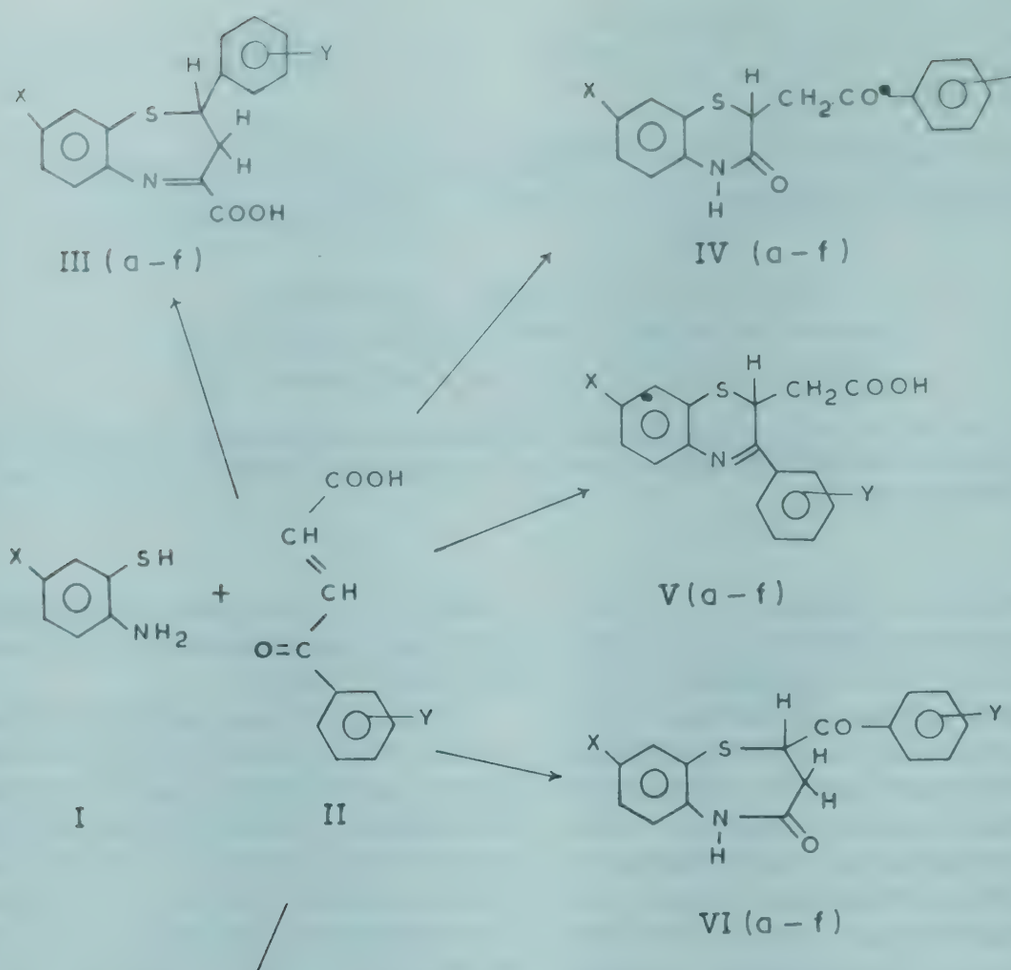
It has been reported that nucleophilic attack by the sulphhydryl electrons of 2-aminothiophenol at β-carbon of α, β-unsaturated ketones or chalkones leads to the formation of Michael type adducts as intermediates which undergo dehydrative cyclization at amino and carboxyl groups to give 2,3-dihydro-1, 5-benzothiazepines[3-5]. The intermediates have been occasionally isolated[3-5] and then cyclised to give final products. In a number of cases the final products were directly obtained without intermediates being isolated.

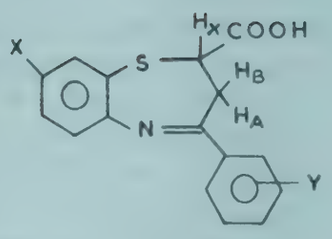
In the present study α, β-unsaturated keto acids (II) reacted with 2-aminothiophenols (Ia,b) to give the title compounds (VII) in one-step (Scheme 1). No intermediate could be isolated in any reaction. The products gave positive tests for carboxylic group but negative tests for carbonyl group. This clearly shows that the formation of VII takes place through cyclisation involving amino and carboxylic groups. This also suggests the formation of an adduct or an intermediate by the nucleophilic attack[3,4,11] of sulphhydryl electrons of I at α-carbon atom of II, and thus mechanistically rules out the formation of the products of the types III-VI (Scheme 1).

Formation of products of the type III is ruled out as it would at first require to undergo nucleophilic attack by the lone pair of electrons of the amino nitrogen of I on α-carbon of II prior to second nucleophilic attack by sulphhydryl electrons[5], whereas, it has been conclusively proved otherwise in analogous reactions. The formation of compounds of the types V and VI would involve nucleophilic attack by sulphhydryl electrons at the β-carbon atom of II. In the absence of any intermediate being isolated in any reaction in this series, no experimental evidence could be provided to indicate relative reactivity at α- and β-carbon atoms especially when there is a carboxyl group at one and a carbonyl group at the other end of the unsaturation in II. However, carbonyl group is expected to exert more pull on the labile π electrons of C_2—C_3 rather than resonance stabilised carboxyl group rendering C-2 an electrophilic centre and C-3 a carbanion.

Further, IR spectral studies and chemical evidences rule out the possibility of structure VI whereas, PMR studies conclusively negate the structure V. IR, PMR, ^{13}CMR and also mass spectral studies not only rule out the probability of structure IV but expediently substantiate the structure VII.

The structures IV and VI can be distinguished by IR spectral studies as IV and VI have two keto groups. It is established that in simple open chain ketones the frequency of carbonyl absorption lies in the range 1725-1706 cm^{-1} provided that no hydrogen bonding and other interference effects occur. Carbonyl group in unstrained saturated rings also absorbs in the same frequency range 1720-1705 cm^{-1}. Aryl group attached directly to carbonyl group lowers the frequency by about 20 cm^{-1} and absorbs at 1700-1680 cm^{-1}. Acetophenone shows the carbonyl absorption at 1686 cm^{-1} and benzalacetophenone which has an al-





VII (a-f)

	X	Y
I;	H, CH_3	–
II;	–	H, 4-CH_3, 4-OCH_3
		4-Cl, 2,4 $(OH)_2$
$III_a - VII_a$;	H	H
$III_b - VII_b$;	H	4-CH_3
$III_c - VII_c$;	H	4-OCH_3
$III_d - VII_d$;	H	4-Cl
$III_e - VII_e$;	H	2,4-$(OH)_2$
$III_f - VII_f$;	CH_3	4-CH_3

iphatic double bond and an aryl ring in conjugation with carbonyl group, absorbs at 1667 cm^{-1} and phenyl methyl ketone shows carbonyl absorption at 1707 cm^{-1}. In the IR spectra of the products VIa-f, the absence of any strong peak in the range 1700-1670 cm^{-1} indicates the absence of aryl alkyl carbonyl group as well as thiazine or thiazepine ring carbonyl group.

Further, there is no characteristic NH stretching in the range 3400-3100, but there is a very broad trough like absorption at 3200-3100 cm^{-1}, typical of carboxylic OH absorption, the lowering of frequency may be due to hydrogen bonding. The absence of characteristic NH stretching absorption negates the possibility of structures IV and VI.

The spectra of VIIa-f showed absorption in the range 1670-1650 cm^{-1} due to intra hydrogen bonded carboxylic CO. The IR peaks at 1670-1650, 1400.1395 (w) and 1230-1210 (s) cm^{-1} may be due to ν(C—O) or δ(OH). The aromatic ν(CH), ν(C=C) and γ(CH) and saturated ν(CH), ν(C—C) and γ(CH) have also been characterized in the products.

Various workers[3,4,12,13] have established the struc-

ture of 1,5-benzothiazepines, obtained by various routes, by PMR spectroscopy. Hunter & Webb[14] have reported PMR study of some substituted 1,5-benzodiazepines and 1,5-benzothiazepines and characterised all the protons of the heterocyclic thiazepine ring of 1,5-benzothiazepine derivatives.

The PMR signals due to methylene and methine protons of VII are expected to be different from those in structure V. Methylene protons in the chain (IV and V), because of free rotation, are expected to have equivalent hydrogens to a great extent, and, although, they may couple with each other, the value of their coupling constants are expected to be much lower than when methylene group is in the ring. The J_{AB} value of 16 Hz indicates that both the hydrogens of methylene are sterically different; H_A is axial and H_B is equatorial. The axial proton, most often, resonates at higher field than the geminal equatorial proton. The chemical inequivalence of H_A (δ3.17.3.30) and H_B(δ3.70-3.80) distinguishes H_A as axial and H_B as equatorial.

Further, H_A couples with H_B to give a doublet with $J_{AB} = 16$ Hz but the presence of a double doublet is due to its coupling with methine proton at C-2 ($J_{AX} = 9$ Hz). Similarly, the H_B proton which resonates at δ3.7-3.8, on coupling with geminal hydrogen, gives a doublet ($J_{AB} = 16$ Hz) and on coupling with methine proton produces a double doublet ($J_{BX} = 8$Hz). The slight difference in the *J* values of J_{AX} and J_{BX} is due to the different conformations of H_A proton.

Methylene protons in the open chain (IV and V) may appear as a double doublet due to coupling of geminal hydrogens and methine proton but these protons are expected to be equivalent because of free rotation. Hence, looking from the mechanistic aspect, structures III and VI are eliminated.

The mass spectra of all the products (VII) exhibited M^+ peaks corresponding to their molecular composition (Table 1). Further, the M^+ peaks were in odd numbers as the compounds possess an odd number of nitrogen atom in accordance to 'nitrogen rule'.

As an illustration, the mass spectrum of VIIb displayed the molecular ion peak at *m/z* 297 (52.6%) and the base peak at *m/z* 178 (100%) due to loss of $CH_3C_6H_4—C=NH$ radical and subsequent migration of hydrogen radical. The base peak might result from the loss of hydrogen atom from a fragment at *m/z* 179(12.0%) and get stabilised in the cyclised form as $C_9H_6SO_2$ *m/z* 178). A prominent peak at *m/z* 149 appeared in mass spectrum due to loss of OH radical from the radical ion $C_8H_6SO_2$ (*m/z* 166). Thus, the fragmentation pattern corresponding to seven-membered heterocyclic ring structure is in agreement with the structure VII.

In order to distinguish between the structures IV and VII, ^{13}C NMR spectral study seemed to be a valuable tool. The ^{13}C NMR signals appearing at δ192-195 in the products (VIa-f) corresponded to the carboxylic carbon, and are in agreement with the literature values[15]. Absence of a signal around δ210 indicates the absence of a keto carbonyl carbon.

It is, therefore, affirmed that the products mentioned above have carboxylic group which also finds confirmation by all other evidences. Thus, on the basis of the above chemical, mechanistic and spectral evidences the products were identified as 4-aryl-2-carboxy-2, 3-dihydro-1, 5-benzothiazepines (VIIa-f) (Table 1).

Experimental Procedure

All melting points are uncorrected. IR spectra in KBr were recorded on a Parkin-Elmer infracord 577 spectrophotometer, PMR spectra in $CDCl_3$ either on a Perkin-Elmer R-12B-60 MHz or a Jeol FT NMR 90 MHz spectrometer and ^{13}C NMR spectra in $CDCl_3$ on a Jeol FT NMR 90 MHz instrument using TMS as internal standard (chemical shifts in δ, ppm) and mass

Table 1—Characterization Data of 4-Aryl-2-carboxy-2,3-dihydro-1,5-benzothiazepines (VII)

Compd	Y	X	Yield (%)	m.p. °C	R_f	Mol. formula (M^+)	Found(%) (Calc.)		
							C	H	N
VIIa	H	H	60	178	0.67	$C_{16}H_{13}NO_2S$ (283)	68.1 (67.8	4.4 4.6	4.9 5.0)
VIIb	4-CH_3	H	65	196	0.62	$C_{17}H_{15}NO_2S$ (297)	68.5 (68.7	4.9 5.1	4.6 4.7)
VIIc	4-OCH_3	H	60	210	0.59	$C_{17}H_{15}NO_3S$ (313)	65.0 (65.2	4.7 4.8	4.5 4.4)
VIId	4-Cl	H	60	188	0.58	$C_{16}H_{12}NO_2SCl$ (317)	60.4 (60.5	3.7 3.8	4.3 4.4)
VIIe	2,4-$(OH)_2$	H	45	262	0.58	$C_{16}H_{13}NO_4S$ (315)	60.9 (61.0	4.0 4.1	— 4.4)
VIIf	4-CH_3	CH_3	65	200	0.62	$C_{18}H_{17}NO_2S$ (311)	68.3 (69.5	5.4 5.5	4.4 4.5

spectra on a Varian Match-7 instrument. The purity of the compounds was checked by TLC on silica gel G using benzene-ethanol-ammonia (7:2:1, upper layer) as irrigant.

β-Aroylacrylic acids (II)

To a mixture of freshly distilled benzene (15.6 ml; 0.20 mol), powdered meleic anhydride (20.58 g; 0.21 mol) and dry CS_2 (300 ml) in a two mecked one litre r.b. flask equipped with a mechanical stirrer and a dropping funnel at 5°, was added in small portions with stirring anhyd. $AlCl_3$ (56.0 g; 0.42 mol). The reaction mixture on work up afforded yellow crystals of β-benzoylacrylic acid (IIa) m.p. 92° (lit.[9], m.p. 93-94°), yield 21.72 g (60%).

By adopting a similar procedure, β-(4-methylbenzoyl)acrylic acid (IIb; m.p. 138° lit.[9], m.p. 138-139°; yield 50%), β-(4-methoxybenzoyl)acrylic acid (IIc; m.p. 129°, lit,[9] m.p. 129-131°; yield 50%), β-(4-chlorobenzoyl)acrylic acid (IId; m.p. 150°; lit,[9] m.p. 156-157°; yield 50%) and β-(2-4-dihydroxybenzoyl)acrylic acid (IIe; m.p. 193°; lit,[9] m.p. 195°; yield 20%) were prepared.

4-Aryl-2-carboxy-2, 3-dihydro-1, 5-benzothiazepines (VIIa-f, Table 1)

2-Aminothiophenol (0.625 g; 0.005 mol) and β-benzoylacrylic acid (IIa; 0.880 g; 0.005 mol) were refluxed with ethanol (10.0 ml) and gl. acetic acid (1.0 ml) for 2 hr when the colour of the mixture changed from light yellow to dark red. The reaction mixture was cooled, the excess of solvent removed under reduced pressure, and the residue crystallized from methanol to give VIIa as colourless crystals, yield 0.99 g (60%), m.p. 178°; TLC: R_f 0.67; MS: *m/z* 283 (M^+); PMR: 3.20 (*dd*, J_{AB} = 16 Hz, J_{AX} = 9Hz, H_A), 3.80 (*dd*, J_{AB} = 16Hz, J_{BX} = 8Hz, H_B), 4.30 (*dd*, J_{AX} = 9 Hz, J_{BX} = 8Hz, H_X), 9.00 (broad 1H, −COOH), 6.82-8.12 (*m*, 9H, Ar-*H*).

By adopting a similar procedure, the compounds VIIb, VIIc, VIId, VIIe and VIIf were prepared in good yields (Table 1). Synthesis of VIId required refluxing for 15-20 min whereas refluxing for 2-3 hr was required in the synthesis of all other compounds.

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Reaction of 1,2-Dihydronaphth[1,2-*d*][3,1]oxazin-2,4(*H*)-dione with *ortho*-Substituted Anilines

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A comparative study of the reactions of 1,2-dihydronaphth[1,2-*d*][3,1]oxazin-2,4(*H*)-dione (1) and 2*H*-3,1-benzoxazin-2,4(*H*)-dione (**8**) (isatoic anhydride) with *ortho*-substituted anilines has been carried out. Condensation of these compounds with 1,2-diaminobenzenes yields the condensed imidazoles and imidazoquinazolinones, while with 2-aminophenol and 2-aminothiophenol condensed oxazoles and thiazoles respectively are formed.

Preparation of 1,2-dihydronaphth[1,2-*d*][3,1]oxazin-2,4(*H*)-dione (**1**), and its reactions with schiff bases and aromatic primary amines resulting in 2,3-dihydro-2,3-diarylbenzo[*h*]quinazolin-4(1*H*)-ones and 1-amino-2-(N-aryl)carbamylnaphthalenes respectively were reported earlier[1]. Reaction of **1** with anilines having a suitable reactive functional group on adjacent carbon lends scope for heterocyclisation leading to hitherto unreported ring systems. Thus, the reaction of **1** with anilines having amino, hydroxy and thiol functions on *ortho* position has been carried out and the results presented in this paper. Condensation of 2*H*-3,1-benzoxazin-2,4(1*H*)-dione (isatoic anhydride) with these amines has also been studied for comparison.

Condensation of **1** with an equimolar proportion of 1,2-diaminobenzene (**2a**)in hot qacetic acid led to a solid which on preparative TLC yielded two compounds (A) and (B). The mass spectrum of (A) showed the molecular ion at *m/z* 259, indicating it to be a 1:1 product, formed by the elimination of elements of carbon dioxide and water. Based on the spectral and analytical data, compound (A) has been characterised as 2-(1-amino-2-naphthyl)benzimidazole (**3a**, Chart 1).

Thus, **1** in its reaction with the diamine, is functioning as a source of 1-aminonaphthalene-2-carboxylic acid, obviating, however the need of strong acid catalysts in the formation of **3a**. The latter was also obtained by the condensation of 1-aminnaphthalene-2-carboxylic acid with 1,2-diaminobenzene in polyphosphoric acid.

Compound (B) has been assigned the structure as benzimidazo[1,2-*c*]benzo[*h*]-quinazolin-6(5*H*)-one (**4a**, Chart 1) on the basis of spectral (mass, IR, PMR) and analytical data. The formation of **3** and **4** may involve the initial nucleophilic attack on C-4 of **1** by one of the amino groups of the diamine followed by ring opening and subsequent imidazole ring formation resulting in an unstable intermediate (5) (Chart 1). While decarboxylation of **5** leads to **3a**, its cyclodehydration results in **4a**.

In the reaction of **1** with 4-substituted-1,2-diaminobenzenes, there is possibility of formation of, apart from the tautomeric 5 (or 6)-substituted 2(1-amino-2-naphthyl)benzimidazole, one or both the isomeric 9(and/or 10)-substituted benzimidazo-[1,2-*c*]benzo[*h*]quinazolin-6(5*H*)-one(s). When condensation of 4-methyl-, 4-chloro- and 4-nitro-1,2-diamino-benzenes was carried out with **1**, two pure crystalline compounds (TLC) could be isolated from each reaction. Based on spectral and analytical data, one of the products could be characterised as the benzimidazole derivative (**3**) (Table 1) and the other as the benzimidazobenzoquinazolinone derivative (**4**) (Table 1). The exact position of the substituent R(CH_3/Cl/NO_2) in **4** could not be determined from the available spectral data.

To ascertain the generality of this reaction, **1** was also condensed with N-benzyl and N-phenyl-1,2-diaminobenzenes (**6a,b**) when 1-benzyl- and 1-phenyl-2-(1-amino-2-naphthyl)benzimidazoles (**7a,b**; Chart 1, Table 1) respectively, characterised by spectral and analytical data, could be isolated. Further, **1** on condensation with 2-aminophenol (**6c**) and 2-aminothiophenol (**6d**) resulted in 2-(1-amino-2-naphthyl)benzoxazole (**7c**) and 2-(1-amino-2-naphthyl)benzothiazole (**7d**) respectively. Reaction of 1-aminonaphthalene-2-carboxylic acid with **6a** and with **6c** in polyphosphoric acid also yielded **7a** and **7c** (Chart 1) respectively, identical with the samples obtained from the reaction of **6** with **1**.

Reaction of isatoic anhydride (**8**) with 1,2-diaminobenzene (**2a**) in refluxing sulfolane[2] was re-

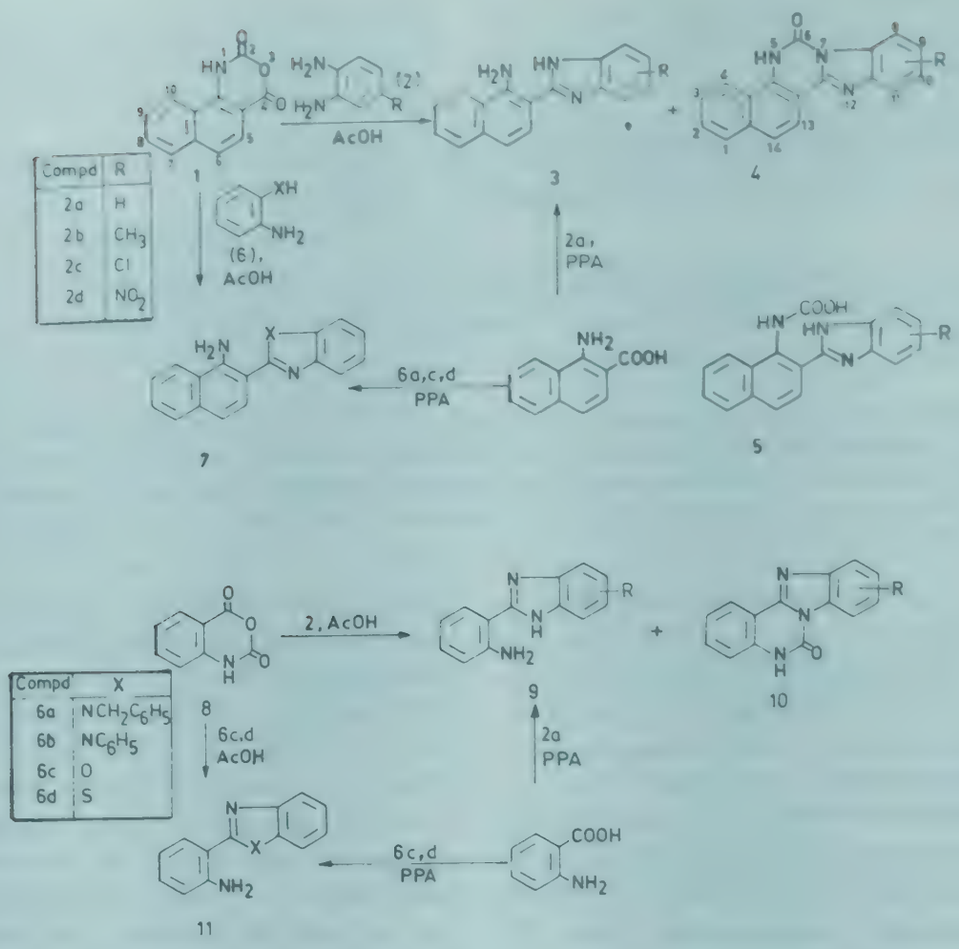

Chart 1

ported to yield 2-(2-aminophenyl)benzimidazole (**9a**) and benzimidazo[1,2-*c*]quinazolin-6(5*H*)-one (**10a**). The above reaction, now carried out in hot acetic acid also resulted in the formation of **9a** and **10a**. We have observed that acetic acid is a better medium as compared to sulfolane in view of the ease of isolation of products and relatively mild conditions employed.

Condensation of isatoic anhydride (**8**) with 4-methyl- and 4-chloro-1,2-diaminobenzenes (**2b,c**) resulted in the corresponding 5(or 6)-substituted-2-(2-aminophenyl)benzimidazoles (**9b,c**; Table 2) and 9(and/or 10)-substituted-benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones (**10b,c**; Table 2). Extension of reaction of **8** to **6c** and **6d** yielded 2-(2-aminophenyl)benzoxazole (**11a**) and 2-(2-aminophenyl)-benzothiazole (**11b**; Chart 1; Table 2) characterised by analogy, spectral and analytical data. Compounds **11a,b** were compared and found to be identical with authentic samples obtained by the reaction of anthranilic acid with **6c,d** in polyphosphoric acid[3]. Thus, both **1** and **8** behaved similarly in their reactions with 1,2-diaminobenzenes, 2-aminophenol and 2-aminothiophenol.

Experimental Procedure

Reaction of 1,2-*dihydronaphth*[1,2-*d*][3,1]*oxazin*-2,4-(1*H*)-*dione* (**1**): (*i*) *With* 1,2-*diaminobenzenes* (**2 & 6**): *General procedure*

A mixture of **1** (0.213 g, 1 mmol) and the appropriate 1,2-diaminobenzene (**2**, 1 mmol) in acetic acid (2 ml) was heated on a steam-bath for 4 hr and left aside. A few drops of ethanol were added to the reaction mxiture to yield a solid which could be separated into 5(or 6)-substituted-2-(1-amino-2-naphthyl)benzimidazole and 9(and/or 10)-substituted-benzimidazo[1,2-*c*]benzo[*h*]-quinazolin-6(5*H*)-one (**3a-d** and **4a-d**; Table 1) by preparative TLC (silica gel G 100-200 mesh) using benzene-EtOAc mixture 10:1 for **3a, 4a**; 14:1 for **3b, 4b**; 9:1 for **3c, 4c**; and 4:1 for **3d, 4d**.

Similar reaction of **1** with N-benzyl and N-pheny-1,2-diaminobenzenes (**6a, b**; X = $NCH_2C_6H_5$ and C_6H_5) yielded the corresponding 1-substituted-2-(1-amino-2-naphthyl)benzimidazoles (**7a,b**). The crude product in each case was chromatographed over a column of neutral alumina using pet. ether (60-80°) – benzene (1:2) as eluent.

Table 1 – Characterisation Data of 2-(1-Amino-2-naphthyl)benzimidazoles (**3** & **7a,b**), Benzoxazole (**7c**), Benzothiazole (**7d**) and Benzimidazo[1,2-*c*]benzo[*h*]-quinazolin-6(5*H*)-ones (**4**)

Compd	R	m.p. (°C)	Yield (%)	Mol. formula (M^+)
3a	H	185	75 66 (in PPA)	$C_{17}H_{13}N_3$ (259)
3b	CH_3	250	71	$C_{18}H_{15}N_3$ (273)
3c	Cl	235	72	$C_{17}H_{12}N_3Cl$ (293)
3d	NO_2	200	65	$C_{17}H_{12}N_4O_2$ (304)
4a	H	230	10	$C_{18}H_{11}N_3O$ (285)
4b	CH_3	185	11	$C_{19}H_{13}N_3O$ (299)
4c	Cl	180	8	$C_{18}H_{10}N_3OCl$ (319)
4d	NO_2 X	298	6	$C_{18}H_{10}N_4O_3$ (330)
7a	$NCH_2C_6H_5$	198	75 68 (in PPA)	$C_{24}H_{19}N_3$ (349)
7b	NC_6H_5	170	70	$C_{23}H_{17}N_3$ (335)
7c	O	172	72 65 (in PPA)	$C_{17}H_{12}N_2O$ (260)
7d	S	260	69 62 (in PPA)	$C_{17}H_{12}N_2S$ (276)

IR(KBr): Compounds **3** displayed ν_{NH} and ν_{NH_2} modes around 3000-3350 cm^{-1}; compounds **4** exhibited $\nu_{C=O}$ (1630 cm^{-1}) and ν_{NH} (3200 cm^{-1}). All the compounds gave satisfactory C, H, and N analyses.
PMR (DMSO-d_6): 4a: δ 7.33-8.39 (10 aromatic H) and 9.8 (NH).

Table 2 – Characterisation Data of 2-(2-Aminophenyl)benzimidazoles (**9**), Benzoxazole (**11a**), Benzothiazole (**11b**) and Benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones (**10**)

Compd	R	m.p. (°C)	Yield (%)	Mol formula (M^+)
9a	H	228	70	$C_{13}H_{11}N_3$ (209)
9b	CH_3	256	65	$C_{14}H_{13}N_3$ (223)
9c	Cl	179	62	$C_{13}H_{10}N_3Cl$
10a	H	300	10	$C_{14}H_9N_3O$ (235)
10b	CH_3	282	9	$C_{15}H_{11}N_3O$ (249)
10c	Cl X	165	6	$C_{14}H_8N_3OCl$
11a	O	126	70	$C_{13}H_{10}N_2O$ (210)
11b	S	150	72	$C_{13}H_{10}N_2S$ (226)

IR(KBr): Compounds **9** exhibited ν_{NH} and ν_{NH_2} around 3300-3500 cm^{-1} and **10** $\nu_{C=O}$ and ν_{NH} around 1670 and 3250 cm^{-1} respectively. All the compounds gave satisfactory C, H and N analyses.

(*ii*) *With* 2-*aminophenol* (**6c**) *and* 2-*aminothiophenol* (**6d**)

To a solution of **1** (0.213 g, 1 mmol) in acetic acid (2 ml) was added **6c** or **6d** (1 mmol) and the reaction mixture heated on a steam-bath for 2 hr. The product that separated upon addition of a few drops of ethanol was filtered and passed through a column of neutral alumina to yield respectively 2-(1-amino-2-naphthyl)benzoxazole (**7c**) and 2-(1-amino-2-naphthyl)benzothiazole (**7d**).

Reaction of 1-*aminonaphthalene*-2-*carboxylic acid*: (*i*) *With* 1,2-*diaminobenzenes* (**2a** and **6a**)

A mixture of 1-aminonaphthalene-2-carboxylic acid (20 mmol) and the appropriate **2a** or **6a** (20 mmol) was added to polyphosphoric acid, freshly prepared by heating phosphorus pentoxide (10 g) and orthophosphoric acid (6 ml, 1.52 d). The reaction mixture was stirred at 230° for 4 hr, cooled to 100° and poured into a large volume of water. The insoluble residue was collected by filtration, washed with water and added to excess of 10% aq sodium carbonate. The product that separated was filtered, washed thoroughly with water, dried at 60° and chromatographed over a column of neutral alumina (eluent, benzene-EtOAc, 1:1) to give pure 2-(1-amino-2-naphthyl)-benzimidazole (**3a**) (66%) and 1-benzyl-2-(1-amino-2-naphthyl)benzimidazole (**7a**) (68%).

(*ii*) *With* 2-*aminophenol* (**6c**) and 2-aminothiophenol (**6d**)

A mixture of 1-aminonaphthalene-2-carboxylic acid (20 mmol) and **6c** or **6d** in polyphosphoric acid (6 ml) was heated at 250° for 4 hr and processed as given above to yield respectively 2-(1-amino-2-naphthyl)benzoxazole (**7c**) (65%) and 2-(1-amino-2-naphthyl)benzothiazole (**7d**) (62%).

Condensation of isatoic anhydride (**8**) *with* 1,2-*diaminobenzenes* (**2**) *in acetic acid*

To a solution of **8** (0.163 g, 1 mmol) in acetic acid (2 ml) was added the appropriate **2** (1 mmol), the reaction mixture heated on a steam-bath for 2 hr and left aside. The crude mixture isolated in each case was separated into 5(or 6)-substituted-2-(2-aminophenyl)benzimidazole (**9**) and 9 (and/or 10)-substituted-benzimidazo[1,2-*c*]quinazolin-6(5*H*)-one (**10**) (Table 2) by preparative TLC using benzene-methanol mixture 9:1 for **9a, 10a;** 12:1 for **9b, 10b** and 10:1 for **9c, 10c.**

Reaction of isatoic anhydride (**8**) *with 2-aminophenol* (**6c**) *and 2-aminothiophenol* (**6d**)

An equimolar mixture of **8** and **6c** or **6d** in acetic acid under similar experimental conditions yielded respectively 2-(2-aminophenyl)benzoxazole (**11a**) and 2-(2-aminophenyl)benzothiazole (**11b**).

Acknowledgement

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Synthesis of the Analogues of Clazamycin

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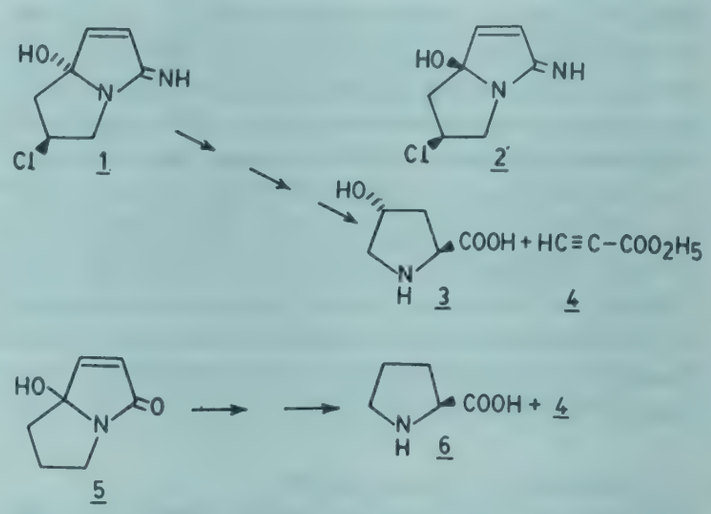
Analogues of clazamycin, 8-hydroxy-5,6,7,8-tetrahydro-3*H*-pyrrolizin-3-one (**5**) and 8-Methoxy-5,6,7,8-tetrahydro-3*H*-pyrrolizin-3-one (**11**) have been synthesized by reacting 1,2-dihydro-3*H*-pyrrolizine (**9**) with singlet oxygen.

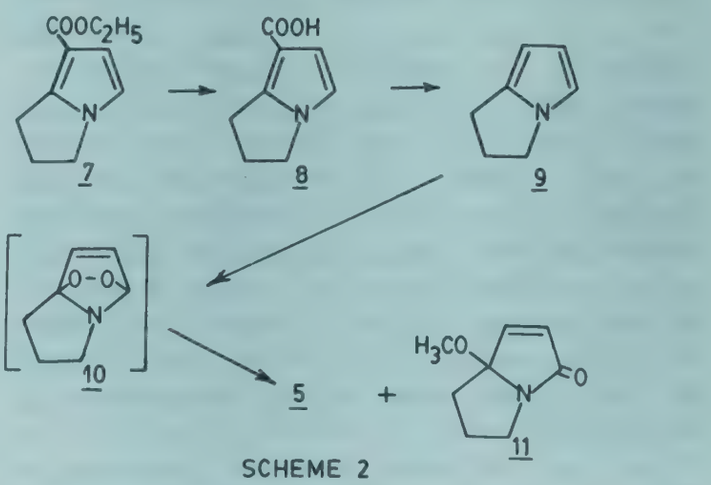
In continuation of our work on anticancer and antibiotic agents of natural origin we came across clazamycin-A (**1**) and clazamycin-B (**2**) which were isolated by Umezawa *et al.*[1] These chlorine containing microbial products attracted our attention because of two interesting features. Firstly, they have pyrrolizidine ring system with vinylamidine function which would undergo facile Michael addition with sulfhydryl group of enzymes involved in important biological processes. Secondly, they have acid labile hydroxyl group.

Retrosynthetic analysis of these clazamycins (Scheme 1) indicated two starting blocks, 4(*R*)-hydroxy-L-proline (**3**) and ethyl propiolate (**4**). But, before attempting the total synthesis of clazamycin it was proposed to attempt the synthesis of its analogues with a view to getting acquainted with their structures and biological activities. Thus, we subjected clazamycin without chlorine and imino groups (**5**) to retrosynthetic analysis which resulted into the starting blocks L-proline (**6**) and ethyl propiolate (**4**) (Scheme 1).



SCHEME 1

As depicted in Scheme 2, N-formyl-L-proline underwent 1,3-dipolar addition with ethyl propiolate in acetic anhydride at reflux, followed by elimination of carbon dioxide to give exclusively the required ethyl 1,2-dihydro-3*H*-pyrrolizine-7-carboxylate (**7**)[2]. After several trials, this ester (**7**) was hydrolysed to the corresponding acid (**8**) by heating at reflux with ethanolic sodium hydroxide. Various attempts to bring about decarboxylation of this acid (**8**) either by heating above its melting point or using quinoline and copper powder remained unsuccessful. Finally, the acid (**8**) was successfully decarboxylated by heating it in 2-aminoethanol at reflux to yield the desired 1,2-dihydro-3*H*-pyrrolizine (**9**). It was also prepared by the method reported by Schweizer and Light[3].



SCHEME 2

At this stage, it was planned to introduce simultaneously two functional groups like hydroxyl and vinyl amide ketone into **9** which can be viewed as equivalent to 1,2-dialkylpyrrole. Though pyrrole is a poor diene for usual dienophiles it accepts some special dienophiles like singlet oxygen[4]. Thus, **9** in methanol was subjected to photo-oxygenation using Rose Bengal as sensitizer to get the endoperoxide which on treatment with platinum black gave a mixture of two products, 8-hydroxy-5,6,7,8-tetrahydro-3*H*-pyrrolizin-3-one (**5**) and 8-methoxy-5,6,7,8-tetrahydro-3*H*-pyrrolizin-3-one (**11**) which could be separated by column

chromatography on silica gel. The analytical and spectral (IR, PMR) data were in agreement with the structures proposed for **5** and **11**.

Experimental Procedure

1,2-Dihydro-3H-pyrrolizine-7-carboxylic acid (**8**)

To a solution of ethyl 1,2-dihydro-3*H*-pyrrolizine-7-carboxylate (**7**) (4 g, 0.022 mol) in ethanol (100 ml) was added a solution of sodium hydroxide (1 g, 0.025 mol) in water (5 ml) and the reaction mixture heated under reflux for 48 hr. The reaction was followed by TLC on silica gel G plates using $CHCl_3$ as irrigant. Solvents were evaporated under suction and 50 ml of water was added to the residue. It was filtered to remove solid particles (if any) and the filtrate acidified with conc. hydrochloric acid. The separated solid was collected by filtration and recrystallised from aq. ethanol as granules (3 g), m.p. 184-85° (d); IR(KBr): 2910 (acidic OH) and 1638 cm^{-1} (C=O); PMR($CDCl_3$, TMS): δ 2.1-2.8 (*m*, 2H), 2.08 (*t*, *J*=7 Hz, 2H), 3.95 (*t*, *J*=7 Hz, 2H), 6.52 (*d*, *J*=2.5 Hz, 1H) and 6.63 (*d*, *J*=2.5 Hz, 1H) (Found: C, 63.5; H, 6.1; N, 9.1, $C_8H_9NO_2$ requires C, 63.4; H, 6.0; N, 9.3%).

1,2-Dihydro-3H-pyrrolizine (**9**)

A mixture of pyrrolizine-7-carboxylic acid (**8**) (2.2 g, 0.014 mol) and freshly distilled 2-aminoethanol (2 ml) was heated in an oil-bath at 175-185° for 15 min when the evolution of CO_2 had ceased. It was cooled to room temperature, poured into 50 ml of ice cold water and the separated oily product extracted with ether (500 ml). The ether extract was washed with saturated $NaHCO_3$ solution, dried (anhyd $MgSO_4$) and ether distilled off. The residue was distilled under diminished pressure to give **9**, b.p. 75-80°/25 mm (lit.[3], b.p. 70°/20 mm), yield 0.5 g; PMR($CDCl_3$, TMS): δ 2.15-2.95 (*m*, 4H), 3.88 (*t*, *J*=7 Hz, 2H), 5.75 (*dd*, *J*=3, 1.5 Hz, 1H), 6.18 (*t*, *J*=3 Hz, 1H) and 6.58 (*dd*, *J*=3, 1.5 Hz, 1H).

Photo-oxygenation of 1,2-dihydro-3H-pyrrolizine: Formation of 8-hydroxy-5,6,7,8-tetrahydro-3H-pyrrolizin-3-one (**5**) *and 8-methoxy-5,6,7,8-tetrahydro-3H-pyrrolizin-3-one* (**11**)

In a 500 ml photochemical reaction vessel were placed **9** (0.25 g, 0.0023 mol), Rose Bengal (5 mg) and methanol (250 ml). The vessel was placed in the center of a cooling bath (acetone/dry ice, −10° to 0°C). The reaction solution was magnetically stirred and irradiated with G.E. 300 W tungsten lamp while oxygen was passed through dispersion disc at the bottom. The disappearance of starting material was followed by TLC (silica gel G plate, ethyl acetate) (5 hr). The reaction mixture was allowed to attain room temperature and methanol distilled under suction at 25-30° to 15 ml. Precipitated platinum black (40 mg) was added to destroy hydroperoxide and the mixture stirred at room temperature for 20 hr. After removal of platinum black, methanol was removed under suction at 25-30° and the residue extracted with ethyl acetate (25 ml). Ethyl acetate extract was chromatographed on silica gel (60-230 mesh, 50 g) using ethyl acetate as eluant to get the desired 8-hydroxylactam (**5**) (R_f 0.36) and 8-methoxylactam (**11**) (R_f 0.6). Further purification was effected by preparative TLC on silica gel plates (6″×6″) using ethyl acetate as irrigant. Their characterization data are as follows.

8-Hydroxy-5,6,7,8-tetrahydro-3H-pyrrolizin-3-one (**5**)

Recrystallised from pet. ether (40-60°) as pale yellow granules, m.p. 94-95°, yield 40 mg; IR($CHCl_3$) 3570 (−OH) and 1698 cm^{-1} (C=O); PMR($CDCl_3$, TMS): δ 1.2-2.7 (*m*, 4H), 3.43 (*m*, 2H), 4.04 (*br*, 1H), 5.96 (*d*, *J*=6 Hz, 1H) and 7.13 (*d*, *J*=6 Hz, 1H) (Found: C, 60.2; H, 6.5; N, 10.0. $C_7H_9NO_2$ requires C, 60.4; H, 6.5; N, 10.1%).

8-Methoxy-5,6,7,8-tetrahydro-3H-pyrrolizin-3-one (**11**)

Liquid, yield 63 mg; IR ($CHCl_3$) 1698 cm^{-1} (C=O); PMR($CDCl_3$, TMS): δ 1.2-2.7 (*m*, 4H), 3.2 (*s*, 3H), 3.5 (*m*, 2H), 6.08 (*d*, *J*=6 Hz, 1H) and 7.04 (*d*, *J*=6 Hz, 1H) (Found: C, 62.5; H, 7.3; N, 9.9. $C_8H_{11}NO_2$ requires C, 62.7; H, 7.2; N, 9.8%).

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A Novel Polymer-Polypeptide Linkage Cleavable with Dithionite†

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5-Bromomethyl-2-nitrobenzoic acid is prepared from 5-methyl-2-nitrobenzoic acid and esterified to polyethyleneglycol 6000 or its amino derivative. The resulting polymers are useful for stepwise peptide synthesis using liquid phase technique. When reacted with Boc-amino acids, these polymers form *p*-nitrobenzyl ester type of linkage. The amino acid is cleaved off the polymers quantitatively by treating with neutral sodium dithionite solution. A model dipeptide L-Leu-L-Val has been synthesized. It has been shown that there is very little racemization during the attachment of valine to the polymers and the subsequent cleavage of this linkage. Another model tetrapeptide Leu-Ala-Gly-Val has been synthesized on the soluble polymers. After cleavage from the polymers, the tetrapeptide on chromatography using an amino acid analyzer, is found to contain only trace amounts of failure sequences, indicating the accessibility of amino groups in successive coupling steps to be very high. The crude tetrapeptide has also been dansylated and subsequently hydrolyzed. TLC analysis shows trace amounts of Dns-Ala, Dns-Gly and Dns-Val in addition to the major spot of Dns-Leu. It is thus concluded that under the normal liquid phase peptide synthesis the amino groups of the polymer-bound amino acids or peptides are freely accessible to coupling reactions. Carboxypeptidase-A digestion of the tetrapeptide removes valine almost quantitatively showing that there is negligible racemization at the valin residue.

Liquid phase peptide synthesis has been developed in an effort to combine the classical synthesis in solution with that of the solid phase method taking the advantages of both[1]. The polymeric protecting group polyethyleneglycol, which is attached through an ester linkage to the carboxyl group of the C-terminal amino acid, imparts solubility to the growing peptide chain in a variety of organic solvents. Thus, all the reactions during synthesis could be done in homogenous solution. Polymer-protected peptide is separated from the reagents and byproducts by crystallization or by dialysis. Polyethyleneglycols of molecular weight 2000-20,000 have been used without any significant influence on the synthetic strategy.

The usual linkage in the liquid phase peptide synthesis is the ester bond[1,2] between the terminal $-OH$ group of polyethyleneglycol and the carboxyl group of the C-terminal amino acid. This bond is cleavable under alkaline conditions at the end of the synthesis[1]. It has however been found that steric hindrance plays an important role in the cleavage and in unfavourable cases the peptide is poorly released by alkaline hydrolysis[3]. Prolonged alkaline hydrolysis is undesirable because it can cause racemization and other side reactions.

In order that the detachment of polypeptide from polyethyleneglycol may be achieved under more desirable conditions, several other linkages between the two have been devised. These include the acid and hydrogenation labile benzyl ester[4] or the *o*-nitrobenzyl ester[5] which is cleaved photolytically. In other modifications of these strategies, the terminal hydroxyl groups of polyethyleneglycol are replaced by amino groups and in suitable situations, the amide linkage which the anchoring group formed with these derivatives of polyethyleneglycol are advantageous over conventional ester linkages[6].

It is known that *p*-nitrobenzyl esters of amino acids are cleaved spontaneously in neutral media if the nitro group is reduced to amine. The reduction can be accomplished either through hydrogenation or with sodium dithionite. Both are attractive methods because deesterification by these methods is done under neutral conditions.

Based on the concept of using this reaction in liquid phase strategy, the key compound 5-bromomethyl-2-nitrobenzoic acid was synthesized and

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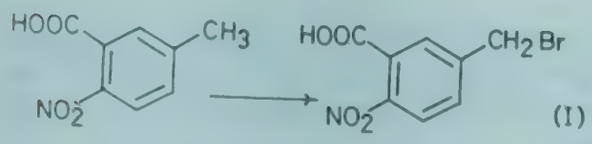
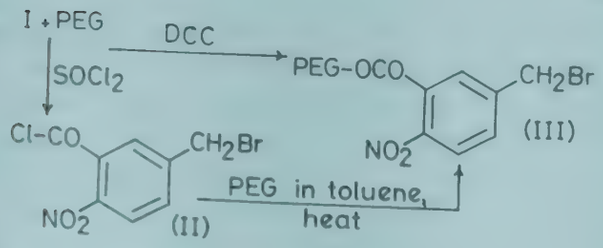
attached to polyethyleneglycol 6000 through the following steps:

5-Methyl-2-nitrobenzoic acid was treated with N-bromosuccinimide in the presence of a small amount of benzoylperoxide in carbon tetrachloride to give 5-bromomethyl-2-nitrobenzoic acid in 95% yield. The resulting compound (I) was then esterified to polyethyleneglycol by either dicyclohexylcarbodiimide or through conversion into 5-bromomethyl-2-nitrobenzoyl chloride by treatment with thionyl chloride and reaction with polyethyleneglycol in a neutral solvent (Scheme 1).

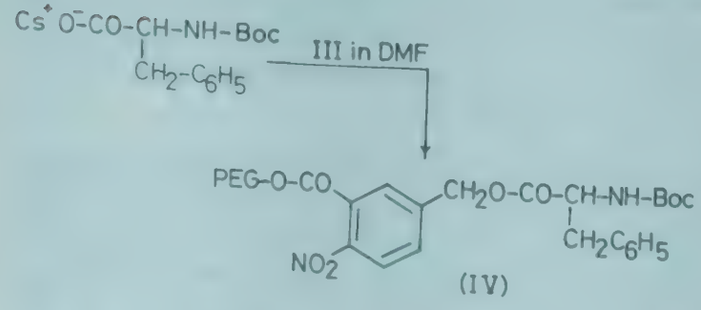
The resulting polymer (III) has an anchoring group to which an N-protected amino acid can be attached through a *p*-nitrobenzyl ester linkage. Thus, when the caesium salt of Boc-phenylalanine was treated with the polymer in dimethylformamide at 50°, esterification was complete in 16 hr[7] to give IV. The purified polymer derivative (IV) on treatment with trifluoroacetic acid in methylene chloride afforded V (Scheme 2) which gave a positive ninhydrin reaction in Kaiser test[8]. The presence of the nitro group increased the acid resistance of the benzyl ester linkage.

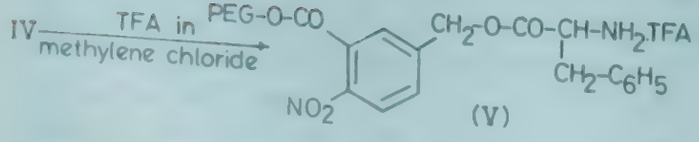
When V was dissolved in 0.5 *M* phosphate buffer at *p*H 7.2 containing 0.2 *M* sodium dithionite,



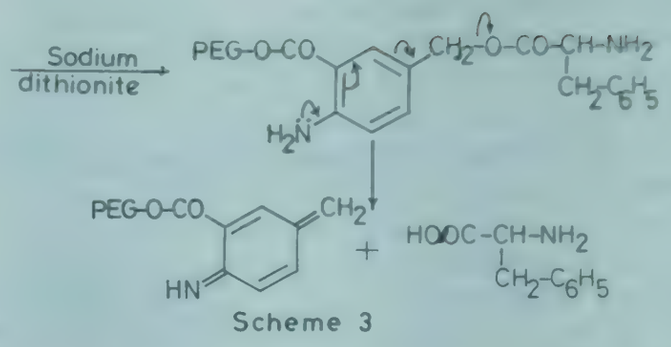


Scheme 1





Scheme 2



Scheme 3

release of phenylalanine (Scheme 3) started at room temperature in less than 0.5 hr and the reaction was complete in about 6 hr. The release of the amino acid was followed on an amino acid analyzer and it was estimated that the amino acid was liberated to the extent of 98-99%. The reaction was faster at higher temperatures and under the optimal conditions the temperature was kept at 40°. By a similar sequence of reactions, Boc-leucine was esterified with polymer III giving Boc-Leu-OCH_2 C_6H_3(4-NO_2-3-CO − OPEG) (VI) which was successfully cleaved by sodium dithionite at neutral *p*H. Since both acids carry bulky side chains, these experiments show that there was no steric hindrance either to the esterification or release of the amino acids.

The same results were obtained when polyethyleneglycol was replaced by its derivative where the terminal hydroxyl groups had been replaced by amino groups.

In an effort to test the suitability of the modified polyethyleneglycol support and cleavage method a model dipeptide was synthesized. The dipeptide polymer ester IX was synthesized by stepwise manner. On hydrolysis and amino acid analysis it was found that the ratio of Leu:Val on the polymer ester was 1:1.

A portion of the dipeptide polymer ester was treated with trifluoroacetic acid. The solvent was removed with a stream of nitrogen and the residue taken in 0.5 *M* sodium phosphate (*p*H 7.2) containing 0.2 *M* sodium dithionite at 30° for 6 hr. Aliquots of this solution were applied to the amino acid analyzer and eluted with 0.2 *M* sodium citrate buffer (*p*H 4.25). Two peaks emerged corresponding to L−Leu−L−Val and L−Leu−D−Val. The latter was less than 0.1% of the former thus showing very little racemization in the process of esterification of valine to the polymer and during reductive cleavage of the dipeptide.

A model tetrapeptide Boc-Leu-Ala-Gly-Val[9] was synthesized stepwise on polymer III or its amino counterpart starting from Boc-Val-polymer

ester. After treatment with trifluoroacetic acid and cleavage from the polymer with sodium dithionite, the crude tetrapeptide was run on an amino acid analyzer and eluted with citrate buffer (*p*H 3.28) (0.2 *M* Na^+). This procedure separated Leu-Ala-Gly-Val from the failure sequences. It was calculated that the tetrapeptide constituted 87.6% of the ninhydrin positive product and demonstrated a fairly high availability of the amino groups in successive coupling steps in liquid phase peptide synthesis using the modified polymers in these experiments.

The crude tetrapeptide was dansylated[10] and the dansylated product hydrolyzed. TLC of the hydrolysate revealed an intense spot of Dns-Leu with traces of Dns-Ala, Dns-Gly and Dns-Val which further confirmed the presence of only very small amonts of failure sequences during the stepwise synthesis.

The crude tetrapeptide was purified by TLC on silica gel-G plates. The purified peptide on hydrolysis, gave the correct ratio for amino acids it contained. When digested with carboxypeptidase-A for 4 hr, all the valine was released as shown by the amino acid analysis of the remaining tripeptide which contained only Leu, Ala and Gly in the ratio 1.01:1.00:0.98. This demonstrated that there was no racemization at the valine residue during esterification of valine onto the polymer and during remvoal of the tetrapeptide by reductive hydrolysis with sodium dithionite.

Experimental Procedure

All melting points are uncorrected. Following abbreviations (in parentheses) have been used: dicyclohexylcarbodiimide (DCC), dimethylformamide (DMF), trifluoroacetic acid (TFA), polyethyleneglycol (PEG) and dicyclohexylurea (DCHU).

5-Bromomethyl-2-nitrobenzoic acid (I)

To 5-methyl-2-nitrobenzoic acid (18.2 g, 0.1 mol) in carbon tetrachloride (100 ml) were added benzoyl peroxide (0.5 g) and freshly recrystallized N-bromosuccinimide (21.4 g, 0.12 mol) and the mixture was refluxed for 4 hr, cooled, filtered and the filtrate evaporated to dryness. The residue was taken in ether, the solution washed with water, dried over anhyd. sodium sulphate and the solvent removed. The product on recrystallization from ether-hexane melted at 180° (Found: C, 36.92; H, 2.3; N, 5.38. $C_8H_6O_4NBr$ requires C, 37.1; H, 2.32; N, 5.4%).

5-Bromomethyl-2-nitrobenzoyl chloride (II)

The acid I (1 g) in dry benzene (10 ml) was refluxed with thionyl chloride (5 ml) for 2 hr under exclusion of moisture. The solvent and excess thionyl chloride were removed under reduced pressure. The residue crystallized on trituration with pet. ether, m.p. 75° (Found: C, 34.53; H, 1.79; N, 5.03. $C_8H_5O_3NClBr$ requires C, 34.5; H, 1.8; N, 5.04%).

5-Bromomethyl-2-nitrobenzoylpolyethyleneglycol (III)

(A) The acid I (3.9 g) and PEG 6000 (10 g) were dissolved in methylene chloride (100 ml) at room temperature and DCC (3.1 g) was added. The mixture was stirred for 24 hr and the precipitated DCHU filtered. The filtrate was treated with acid I (3.9 g)and DCC (3.1 g) again for two days. DCHU was filtered off and the filtrate concentrated. To this solution ether was added with stirring. The product which precipitated was collected, washed with ether and recrystallized from ethanol, yield 9.5 g.

(B) PEG (10 g) was taken in dry toluene and II (5 g) added to it. The solution was refluxed for 10 hr while a slow stream of dry nitrogen passed through it to remove the HCl formed. The solvent was removed, the residue taken in methylene chloride and the product precipitated by the addition of ether. It was recrystallized several times from ethanol.

Esterification of Boc-phenylalanine with PEG derivative III: Formation of IV

A mixture of PEG derivative III (1 g)and Boc-Phe-O^-Cs^+ (0.4 g) in DMF (5 ml) was stirred at 50° for 24 hr. The solvent was removed under diminished pressure, and the residue taken in methylene chloride and filtered. The filtrate was concentrated, the product precipitated with ether and recrystallized from ethanol. Amino acid analysis gave Phe = 0.12 mmol/g.

Treatment of IV with TFA: Formation of V

The PEG derivative IV (0.5 g) was dissolved in 50% TFA in methylene chloride and left at room temperature for 30 min. An excess of ether was then added gradually and the precipitate collected by filtration, and recrystallized from ethanol.

Reductive release of phenylalanine from PEG derivative V

The PEG derivative V (0.2 g) was dissolved in 0.5 *M* phosphate buffer containing 0.2 *M* sodium dithionite (*p*H 7.2), and the solution left at room temperature. It was checked from time to time for the release of phenylalanine on TLC (silica gel;

n-butanol-AcOH-H_2O, 4:1:1) which was sprayed with ninhydrin. Detectable amounts of phenylalanine appeared in half an hour. Thereafter, aliquots were taken out at half-hourly intervals and phenylalanine was estimated on an amino acid analyzer. It reached its maximum value at the end of six hours and was estimated at 98-99% of the theoretical value.

Esterification of Boc-leucine with PEG derivative III: Formationof (VI)

The reaction was carried out in the same manner as described for the esterification of Boc-phenylalanine with the polymer. Amino acid analysis gave Leu = 0.11 mmol/g.

Removal of Boc-group from VI: Formation of VII

PEG derivative VI was treated with TFA by the same method as described for the corresponding phenylalanine derivative IV.

Reductive release of leucine from VII

The PEG derivative VII was treated with sodium dithionite in phosphate buffer as described for V. TLC examination showed that leucine started appearing in half an hour and was released to the extent of 98-99% at the end of six hours as determined from amino acid analysis.

Preparation of aminopolyethyleneglycol (VIII) (Replacement of terminal hydroxyl groups of PEG with amino groups)

(i) PEG 6000 (10 g) in toluene (100 ml) was treated with phosphorus tribromide (4 g). The solution was heated at 70° for 24 hr, concentrated and diluted with ether. The precipitate was collected by filtration, dissolved in toluene, reprecipitated by the addition of ether and recrystallized from ethanol.

(ii) The bromide derivative as obtained above was dissolved in DMF (100 ml) and heated with potassium phthalimide (5 g) at 70° for 20 hr. The solution was concentrated *in vacuo*, diluted with excess ether and the precipitate recrystallized thrice from ethanol.

(iii) The phthalimido derivative was dissolved in warm ethanol. Hydrazine hydrate (4 g) was then added and the solution kept at 60° for 10 hr. On concentrating the solution, aminopolyethyleneglycol separated out and was recrystallized from ethanol (9.4 g).

Boc-Leu-Val-$OCH_2 \cdot C_6H_3$(4-NO_2-3-$CO-O-PEG$) (IX)

(i) Boc-Val-O^-Cs^+ (3 g) and PEG derivative III (10 g) were taken in DMF (5 ml) and the solution was stirred at 50° for 24 hr. The solution was filtered, the filtrate concentrated and a large excess of ether added to it. The precipitate was dissolved in methylene chloride and reprecipitated by adding sufficient ether. It was recrystallized from ethanol. Amino acid analysis gave Val = 0.1 mmol/g.

(ii) The product from the first step was dissovled in a 50% solution of TFA in methylene chloride. After keeping the solution for 30 min at room temperature, an excess of ether was added to it to precipitate the product which was recrystallized from ethanol.

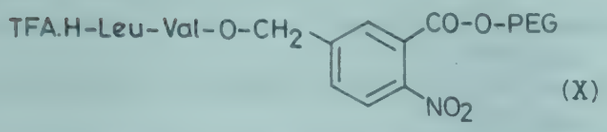
(iii) Boc-leucine (5.5 mmol, 1.27 g) was dissolved in 15 ml of methylene chloride. To the cooled solution at 0° was added a precooled solution of DCC (2.75 mmol, .566 g) in methylene chloride (15 ml). The mixture was allowed to stand at 0° for 1 hr and directly filtered into a solution of the product from the preceeding step in 10 ml of methylene chloride. The solution was neutralized with N-methylmorpholine as checked with a moistened *p*H paper. Stirring was continued for 3 hr. Thereafter, the solution was totally negative to Kaiser test with ninhydrin. The product was precipitated by slow addition of ether and finally recrystallized from ethanol. Amino acid analysis showed the presence of Leu and Val in 1:1.02 molar ratio.

5-Bromomethyl-2-nitrobenzamidopolyethyleneglycol (XI)

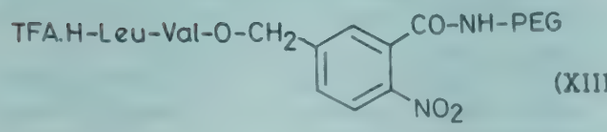
To a solution of acid I (3.9 g) and aminopolyethyleneglycol VIII (10 g) in DMF (20 ml) was added DCC (3.1 g) and the mixture stirred at 0-5° for 3 hr at the end of which it gave a negative response to Kaiser reagent. After stirring at room temperature for 17 hr, the precipitated DCHU was removed by filtration and the filtrate concentrated on a rotavapor. The PEG derivative (XI) was precipitated with ether and recrystallized from ethanol.

Boc-Leu-Val-$OCH_2 \cdot C_6H_3$(4-NO_2-3-$CO-NH-PEG$) (XII)

Boc-valine was esterified to XI through the cae-



(X)



(XIII)

sium salt method which was then converted into XII following the same procedure as described for the preparation of IX. The purified product on hydrolysis and amino acid analysis gave Leu:Val as 1:1.01.

TFA·H-Leu-Val-OCH_2·C_6H_3(4-NO_2-3-CO−O−PEG)(X)

Polyethyleneglycol derivative IX (0.2 g) was dissolved in methylene chloride (0.5 ml) and TFA (0.5 ml) added to it. After 30 min the solution was dried with a stream of dry nitrogen gas and the residue recrystallized from methylene chloride-ether. The product gave a positive colour test with Kaiser reagent.

Sodium dithionite treatment of X, release of the dipeptide

The dipeptidyl derivative (X) of PEG (100 mg) was dissolved in 0.5 *M* phosphate buffer containing 0.2 *M* sodium dithionite (*p*H 7.2). The solution was left at 30° for 6 hr. A portion of the solution was neutralized and applied to the amino acid analyzer. The column was eluted with 0.2 *M* sodium citrate buffer (*p*H 4.25) at 65° at the rate of 8.3 ml/min. L-Leu-D-Val and L-Leu-L-Val emerged at 35 min 40 sec and 39 min 57 sec respectively. The amount of the former was 0.08% of the latter.

TFA·H-Leu-Val-OCH_2·C_6H_3(4-No_2-3-CO−NH−PEG)(XIII)

The aminopolyethyleneglycol derivative XII was treated with 50% TFA in methylene chloride for the removal of Boc-group in the same manner as described under the preparation of X. The product gave a positive Kaiser test.

Sodium dithionite treatment of XIII, release of the dipeptide

The aminopolyethyleneglycol derivative XIII was treated with sodium dithionite in phosphate buffer and the dipeptide analysed on an amino acid analyzer in the same way as described for X. It showed that the diastereoisomer-L-Leu-D-Val was 0.07% of L-Leu-L-Val in the released dipeptide.

Boc-Leu-Ala-Gly-Val-OCH_2·C_6H_3(4-NO_2-3-CO−O−PEG)(XIV)

Boc-Val was attached to the polymer III (10 g) by reaction with Boc-Val-O^-Cs^+ in the usual manner and Boc-group removed by treatment with 50% TFA in CH_2Cl_2. The peptidyl ester XIV was synthesized by stepwise coupling with appropriate Boc-amino acids in the manner described for IX.

Leu-Ala-Gly-Val(XV)

The ester XIV was treated with 50% TFA in methylene chloride. After removing the solvent under reduced pressure, the peptide was cleaved off the polymer by treating with 0.5 *M* phosphate buffer containing 0.2 *M* sodium dithionite (*p*H 7.2) for 6 hr at room temperature. The mixture was then chromatographed on Sephadex G-25 column and the ninhydrin positive fractions were pooled and lyophilized to obtain XV as a powder.

Characterization of the tetrapeptide

TLC of the crude tetrapeptide was performed on silica gel-G plates in two separate systems [*n*-butanol-acetic acid-ethyl acetate-water (1:1:1:1) and *n*-butanol-acetic acid-water (4:1:1)]. A section of the plate was visualized with ninhydrin and the major component scraped, eluted and lyophilized. When applied to an amino acid analyzer and eluted with citrate buffer *p*H 3.28 (0.2 *M* Na^+), it emerged at 90 min.

A portion of TLC purified tetrapeptide was hydrolyzed. Amino acid analysis gave leu, 1.02; Ala, 1.00; Gly, 1.01 and Val, 0.98.

A small amount of the crude tetrapeptide was run on the amino acid analyzer under the same conditions. The ninhydrin positive elution profile gave three minor and one major peaks. The major peak (87.6%) emerged at 90 min and was thus due to Leu-Ala-Gly-Val.

The crude tetrapeptide (60 nanomoles) was dansylated and hydrolyzed. The hydrolyzate was subjected to two-dimensional chromatography on polyamide layer sheets first in water-formic acid (300:4.5) and then in benzene-acetic acid (270:30). The major spot corresponded to Dns-Leu and there were only traces of Dns-Ala, Dns-Gly and Dns-Val.

A portion of the purified tetrapeptide was treated with carboxypeptidase-A for 4 hr at 37°. The mixture was lyophilized, redissolved in a few drops of water and chromatographed on a silica gel plate by the method described above. One of

the components was identified as valine and the other on hydrolysis and amino acid analysis, showed the presence of Leu, Ala and Gly in the ratio 1.01:1.00:0.98 but no Val.

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Studies in Nucleosides: Part XVIII—Synthesis of 6-Methoxy/methylthio-4-N-substituted-1-(2′-tetrahydropyranyl/2′-hydroxyethoxymethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidines & Their Biological Activity†

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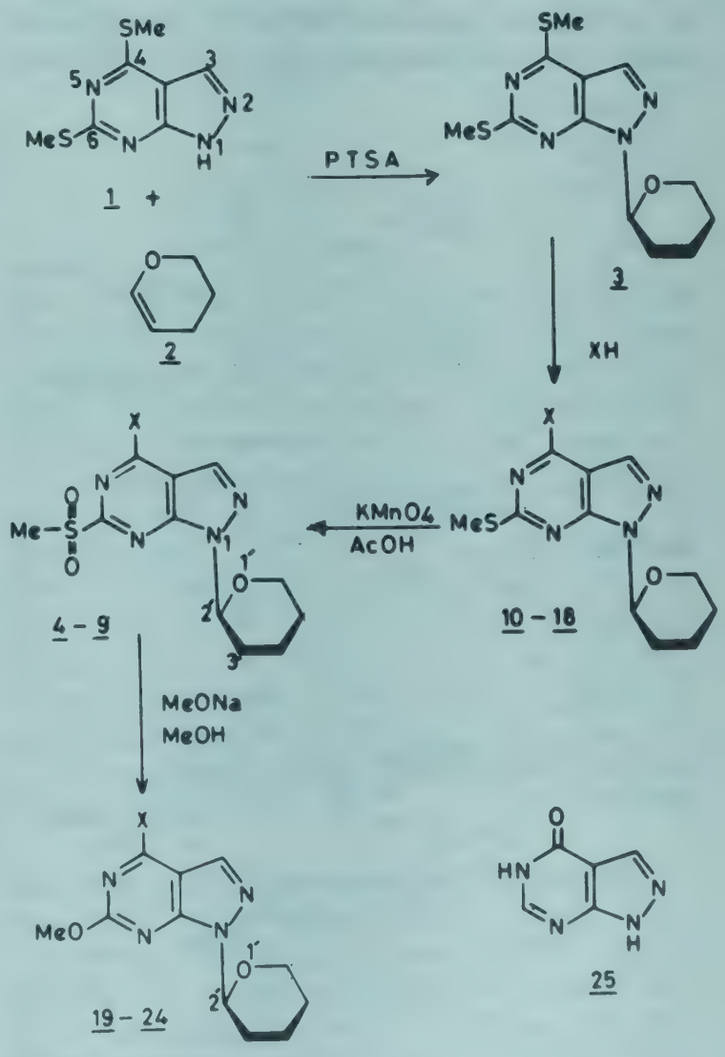
6-Methylthio-4-N-substituted-1-(2′-tetrahydropyranyl)-1*H*-pyrazolo[3,4-*d*]pyrimidines (**10-18**), the corresponding sulphones (**4-9**), 6-methoxy-4-N-substituted-1-(2′-tetrahydropyranyl)-1*H*-pyrazolo[3,4-*d*]pyrimidines (**19-24**), 4-amino-6-methylthio-1-(2′-hydroxyethoxymethyl)pyrazolo[3,4-*d*]pyrimidine (**28**) and 4-amino-6-methoxy-1-(2′-hydroxyethoxymethyl)pyrazolo[3,4-*d*]pyrimidine (**33**) have been synthesized. The compounds **10-24** when tested for their antiallergic activity, show significant passive cutaneous anaphylaxis (PCA) activity. Of the compounds **10-31** and **33** screened against the Ranikhet disease virus (RDV), the compounds **7** and **31** exhibit 80 and 90% inhibition respectively.

Abnormal purine metabolism causes a number of human diseases and specific inhibitors of purine metabolizing enzymes are found effective in the treatment of some of the diseases. Allopurinol (**25**), a substituted pyrazolo[3,4-*d*]pyrimidine, is being clinically used in the treatment of gout and in other conditions of rapid purine catabolism[1]. There are several reports which suggest that 4-amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine and related compounds may function as a substrate for anabolic[2-4] and catabolic enzymes[5,6]. Several 1-tetrahydropyranyl-1*H*-pyrazolo[3,4-*d*]pyrimidines have also been found to have significant anticancer activity[7]. These reports prompted us to undertake the synthesis of some substituted pyrazolo[3,4-*d*]pyrimidines. In the present paper we report the syntheses of 6-methylthio-4-N-substituted-1-(2′-tetrahydropyranyl)pyrazolo[3,4-*d*]pyrimidines (**10-18**), 6-methylsulphonyl-4-N-substituted-1-(2′-tetrahydropyranyl)pyrazolo[3,4-*d*]pyrimidines (**19-24**) which may act as pro-drug[8], and 4-amino-6-methoxy-1-(2′-hydroxyethoxymethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**33**) as spongosine (**32**) analogue[9]. The antiallergic and antiviral activities of the compounds synthesized have also been reported.

Condensation of 4,6-dimethylthiopyrazolo[3,4-*d*]-pyrimidine (**1**) (Scheme 1) with 2,3-dihydropyran (**2**) afforded 4,6-dimethylthio-1-(2′-tetrahydropyranyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**3**) in 93% yield. The reaction of **3** with various amines yielded 6-methylthio-4-N-substituted-pyrazolo[3,4-*d*]-pyrimidines (**10-18**). Oxidation of **13-18** with $KMnO_4$ in the presence of acetic acid afforded



SCHEME 1

the corresponding sulphones (**4-9**) which on further reaction with sodium methoxide gave 6-methoxy-4-N-substituted-1-(2′-tetrahydropyranyl)1*H*-pyrazolo[3,4-*d*]pyrimidines (**19-24**) in fairly good yield.

†CDRI Communication No. 3960

Condensation of **1** (Scheme 2) with benzoyloxyethoxymethylchloride (**26**) gave 1-(2′-benzoyloxyethoxymethyl)-4,6-dimethylthiopyrazolo[3,4-*d*]pyrimidine (**27**). Deblocking of **27** with methanolic ammonia at ambient temperature yielded 4,6-dimethylthio-1-(2′-hydroxyethoxymethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**29**). Treatment of **29** with methanolic ammonia at 120° in a steel bomb gave 4-amino-1-(2′-hydroxyethoxymethyl)-6-methylthiopyrazolo[3,4-*d*]pyrimidine (**28**) which on acetylation with acetic anhydride and pyridine afforded the diacetyl derivative (**30**). Oxidation of **30** with $KMnO_4$ in the presence of acetic acid gave the sulphone (**31**) which on refluxing with excess of MeONa in methanol finally afforded 4-amino-1-(2′-hydroxyethoxymethyl)-6-methoxypyrazolo[3,4-*d*]pyrimidine (**33**) in 85% yield.

Compound **10-24** were subjeted to passive cutaneous anaphylaxis (PCA) test for their antiallergic activity. The test was performed according to the procedure described earlier[10]. Mepyramine maleate (an antihistamine agent) and disodium chromoglycate (an antiallergic drug) were used as reference standards. The screening results are recorded in Table 1. Compounds **10-24** showed 48, 71, 49, 65, 26, 64, 54, 54, 65, 61, 71, 71, 71, 71 and 71% of PCA inhibition respectively at 50 mg/kg in mice.

The compounds **4-31** and **33** were tested at 0.1 mg/ml/culture against the Ranikhet disease virus (RDV) (0.064 HA/ml) *in vitro* according to the procedure described earlier[11]. The results of antiviral screening are summarised in Table 2. Compounds **7, 9, 11, 18, 23** and **31** exhibited 80, 50, 50, 70, 50 and 90% inhibition respectively. The remaining compounds either showed low activity or were found inactive.

Experimental Procedure

For general directions see earlier paper in the series[12]. PMR, IR and elemental analyses data of the compounds (cf. Table 1) were in conformity with the assigned structures.

4,6-Dimethylthio-1-(2′-tetrahydropyranyl)-1H-pyrazolo[3,4-d]pyrimidine (**3**)

A solution of 4,6-dimethylthiopyrazolo[3,4-*d*]-pyrimidine[13] (**1**; 5 g, 24 mmol) in dry EtOAc (100 ml) was added to dihydropyran (**2**; 7 g, 80 mmol) containing *p*-toluenesulphonic acd (PTSA) (0.15 g). The mixture was heated at 50° for 3 hr, cooled, washed with aq. K_2CO_3 solution, water and dried (Na_2SO_4). Ethylacetate was removed *in vacuo* and the product crystallised from ether-hexane to give **3** yield 6.5 g (93%), m.p. 102°; MS: *m/z* 296 ($M^{+\cdot}$); PMR($CDCl_3$): δ 7.86 (*s*, 1H, H-3), 5.86 (*dd*, 1H, H-2′, J = 10 and 2 Hz), 4.1-3.6 (*m*, 2H, OCH_2), 2.56 (*s*, 3H, SCH_3), 2.5 (*s*, 3H, SCH_3), 2.4-1.3 (*m*, 6H, CH_2) (Found: C, 48.3; H, 5.6; N, 18.7. $C_{12}H_{16}N_4OS_2$ requires C, 48.6; H, 5.4; N, 18.9%).

4-Amino-1-(2′-tetrahydropyranyl)-6-methylthio-1H-pyrazolo[3,4-d]pyramidine (**13**)

A mixture of methanolic ammonia (10 ml, MeOH saturated with NH_3 at 0°) and **3** (2 g, 6 mmol) was heated at 120° in a steel bomb for 8 hr and concentrated under reduced pressure. The crude product, thus obtained, was chromatographed on SiO_2 gel (180 g) column. Elution with $CHCl_3$–MeOH (98 : 2, v/v) gave **13**, yield 1.2 g (70%), m.p. 172°; MS: *m/z* 265 ($M^{+\cdot}$); PMR($CDCl_3$): δ 7.73 (*s*, 1H, H-3), 6.2-5.7 (*m*, 3H, NH_2 and H-2′), 4.3-3.6 (*m*, 2H, OCH_2), 2.5 (*s*, 3H, SCH_3), 2.2-1.3 (*m*, 6H, CH_2) (Found: C, 49.6; H, 5.8; N, 26.6. $C_{11}H_{15}N_5OS$ requires C, 49.7; H, 5.7; N, 26.4%).

Table 1—Physical Constants, Yield and Biological Screening Data of 4,6-Disubstituted-pyrazolo-[3,4-*d*]pyrimidines (**4-24**)

Compd	X	Mol. formula	m.p. °C	Yield (%)	% Inhibition of RDV	% PCA inhibition at 50 mg/kg
4	Amino	$C_{11}H_{15}N_5O_3S$	194	68	36	—
5	Methylamino	$C_{12}H_{17}N_5O_3S$	162	78	40	—
6	N,N-Dimethylamino	$C_{13}H_{19}N_5O_3S$	152	81	inactive	—
7	Piperidino	$C_{16}H_{23}N_5O_3S$	144	56	80	—
8	Morpholino	$C_{15}H_{21}N_5O_4S$	194	66	inactive	—
9	2-Phenylethylamino	$C_{19}H_{23}N_5O_3S$	170	77	50	—
10	Hydrazino	$C_{11}H_{16}N_6OS$	164	39	inactive	48
11	*p*-Methylphenylethylamino	$C_{20}H_{25}N_5OS$	104	60	50	71
12	N^4-Phenylpiperizynyl	$C_{21}H_{26}N_6OS$	195	70	inactive	49
13	Amino	$C_{11}H_{15}N_5OS$	172	70	—	65
14	Methylamino	$C_{12}H_{17}N_5OS$	165	82	26	26
15	N,N-Dimethylamino	$C_{13}H_{19}N_5OS$	173	70	inactive	64
16	Piperidino	$C_{16}H_{23}N_5OS$	93	75	30	54
17	Morpholino	$C_{15}H_{21}N_5O_2S$	160	68	inactive	54
18	2-Phenylethylamino	$C_{19}H_{23}N_5OS$	108	67	70	65
19	Amino	$C_{11}H_{15}N_5O_2$	215	71	inactive	61
20	Methylamino	$C_{12}H_{17}N_5O_2$	172	78	30	71
21	N,N-Dimethylamino	$C_{13}H_{19}N_5O_2$	106	73	inactive	71
22	Piperidino	$C_{16}H_{23}N_5O_2$	98	70	inactive	71
23	Morpholino	$C_{15}H_{21}N_5O_3$	150	87	50	71
24	2-Phenylethylamino	$C_{19}H_{23}N_5O_2$	108	70	inactive	71
Mepyramine maleate		—	—	—	—	79 at 25 mg/kg
Disodiumglycate		—	—	—	—	25 at 50 mg/kg

The compounds **10-12** and **14-18** (Table 1) were prepared similarly from **3** using appropriate amines.

4-Amino-6-methylsulphonyl-1-(2′-tetrahydropyranyl)-1H-pyrazolo[3,4-d]pyrimidine (**4**)

To a solution of **13** (1.7 g, 6 mmol) in gl. acetic acid (18 ml) at 0° was added gradually $KMnO_4$ (1.9 g, 12 mmol) and the mixture stirred at 0° for 1 hr and then at ambient temperature for another 1 hr. H_2O_2 was added till the colour of the solution disappeared. The colourless solution was neutralised with $NaHCO_3$, extracted with EtOAc, washed with water, dried (Na_2SO_4) and the solvent removed. The product was crystallised from EtOAc-hexane to give **4**, yield 1.3 g (68%), m.p. 194°; MS: *m/z* 297 ($M^{+\cdot}$); PMR($CDCl_3$ + DMSO-d_6): δ 8.3-7.8 (*bs*, 2H, NH_2), 8.2 (*s*, 1H, H-3), 5.86 (*dd*, 1H, H-2′, *J* = 10 and 2 Hz), 4.1-3.5 (*m*, 2H, OCH_2), 3.2 (*s*, 3H, SO_2CH_3), 2.2-1.3 (*m*, 6H, CH_2) (Found: C, 44.2; H, 5.1; N, 23.8. $C_{11}H_{15}N_5O_3S$ requires C, 44.4; H, 5.1; N, 23.6%).

The compounds **5-9** (Table 1) were prepared similarly from **14-18** respectively.

4-Amino-6-methoxy-1-(2′-tetrahydropyranyl)-1H-pyrazolo[3,4-d]pyrimidine (**19**)

A mixture of **4** (1.1 g, 3 mmol), abs. MeOH and 1*N* MeONa (.5 g, 10 mmol) was refluxed for 5 hr, cooled, neutralised with acetic acid, solvent evaporated and the residue extracted with ethylacetate. The extract was washed with water, dried (Na_2SO_4), solvent removed, and the crude product chromatographed over SiO_2 gel (120 g) column. Elution with $CHCl_3$ – MeOH (95:5, v/v) gave **19**, yield 0.65 g (71%), m.p.215°; MS: *m/z* 249 ($M^{+\cdot}$); PMR($CDCl_3$): δ 7.9 (*s*, 1H, H-3), 5.66 (*dd*, 1H, H-2′, J = 10 and 2 Hz), 4.2-3.5 (*m*, 2H, OCH_2), 3.8 (*s*, 3H, OCH_3), 2.4-1.3 (*m*, 6H, CH_2) (Found: C, 53.2; H, 5.8; N, 28.4. $C_{11}H_{15}N_5O_2$ requires C, 53.0; H, 6.1; N, 28.1%).

The compounds **20-24** (Table 1) were prepared similarly from **5-9**.

1-(2′-Benzoyloxyethoxymethyl)-4,6-dimethylthiopyrazolo[3,4-d]pyrimidine (**27**)

A mixture of **1** (5 g, 24 mmol), DMF (125 ml) and Et_3N (20 g, 198 mmol) was stirred at 10-15°. To it was added dropwise a solution of benzoyloxyethoxymethyl chloride (**26**) (20 g, 90 mmol) in DMF (20 ml) and the mixture stirred at ambient temperature for 12 hr. The excess of solvent and reagent were removed under reduced pressure. The residue was extracted with EtOAc, washed with water, dried (Na_2SO_4), concentrated *in vacuo*, and the crude product chromatographed

on SiO_2 gel (200 g) column. Elution with $CHCl_3$ – EtOAc (98:2, v/v) afforded **27**, yield 5.5 g (60%), m.p. 72°; MS (*m/z*): 390 ($M^{+\cdot}$); PMR($CDCl_3$): δ 8.0-7.6 (*m*, 3H, H-3 and Ar – *H*) 7.5-7.0 (*m*, 3H, Ar – *H*), 5.6 (*s*, 2H, N – CH_2O), 4.5-3.6 (*m*, 4H, CH_2CH_2), 2.5 (*s*, 3H, SCH_3), 2.4 (*s*, 3H, SCH_3) (Found: C, 52.2; H, 4.5; N, 14.6. $C_{17}H_{18}N_4O_3S_2$ requires C, 52.3; H, 4.6; N, 14.3%).

4,6-*Dimethylthio*-1-(2′-*hydroxyethoxymethyl*)-*pyrazolo*[3,4-*d*]*pyrimidine* (**29**)

A mixture of **27** (2.5 g, 6 mmol) and methanolic ammonia (60 ml, MeOH saturated with NH_3 at 0°) was kept at ambient temperature for 24 hr. The solvent and excess of reagent were removed and the residue was chromatographed over SiO_2 gel (180 g) column. Elution with $CHCl_3$ – MeOH (98:2, v/v) gave **29**, yield 3.2 (87%), m.p. 85°; MS: *m/z* 286 ($M^{+\cdot}$); PMR($CDCl_3$): δ 7.83 (*s*, 1H, H-3), 5.66 (*s*, 2H, N – CH_2 – O), 3.9 (*s*, 4H, $CH_2 - CH_2$), 2.56 (*s*, 3H, SCH_3), 2.46 (*s*, 3H, SCH_3) (Found: C, 42.1; H, 4.7; N, 19.8. $C_{10}H_{14}N_4O_2S_2$ requires C, 41.9; H, 4.9; N, 19.6%).

4-*Amino*-6-*methylthio*-1-(2′-*hydroxyethoxymethyl*)-*pyrazolo*[3,4-*d*]*pyrimidine* (**28**)

A mixture of **29** (1.4 g, 4 mmol) and methanolic ammonia (60 ml, MeOH saturated with NH_3 at 0°) was heated in a steel bomb at 120° fr 24 hr and the solvent and excess of reagent were removed under reduced pressure. The residue was extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and solvent removed. The product was crystallised from MeOH – EtOAc to give **28**, yield 1 g (85%), m.p. 176°; MS: *m/z* 255 ($M^{+\cdot}$); PMR(DMSO-d_6): δ 8.4 (*s*, 1H, H-3), 7.8-7.3 (*bs*, 2H, NH_2), 5.96 (*s*, 2H, N – CH_2), 3.93 (*s*, 4H, $CH_2 - CH_2$), 2.8 (*s*, 3H, SCH_3) (Found: C, 42.4; H, 5.4; N, 27.4. $C_9H_{13}N_5O_2S$ requires C, 42.3; H, 5.1; N, 27.4%).

4-*Acetamido*-1-(2′-*acetoxyethoxymethyl*)-6-*methylthiopyrazolo*[3,4-*d*]*pyrimidine* (**30**)

A mixture of **28** (0.7 g, 2.7 mmol), acetic anhydride (2 g, 19 mmol) and pyridine (12 ml) was stirred for 24 hr at ambient temperature, the excess of reagent removed under reduced pressure, and the residue extracted with chloroform, washed with aq. $NaHCO_3$, water, dried (Na_2SO_4) and solvent removed. The crude product was chromatographed over SiO_2 gel (120 g) column. Elution with $CHCl_3$ – MeOH (95:5, v/v) gave **30**, yield 0.7 g (76%), m.p. 158°; MS: *m/z* 339 ($M^{+\cdot}$); PMR($CDCl_3$): δ 8.46 (*s*, 1H, H-3), 5.7 (*s*, 2H, N – CH_2 – O), 4.45-3.6 (*m*, 4H, $CH_2 - CH_2$), 2.5 (*s*, 3H, SCH_3), 2.20 (*s*, 3H, $COCH_3$), 1.9 (*s*, 3H, $COCH_3$) (Found: C, 46.4; H, 5.4; N, 20.7. $C_{13}H_{17}N_5O_4S$ requires C, 46.0; H, 5.0; N, 20.6%).

4-*Acetamido*-1-(2′-*acetoxyethoxymethyl*)-6-*methylsulphonylpyrazolo*[3,4-*d*]*pyrimidine* (**31**)

Compound **30** (0.6 g, 1.7 mmol) in acetic acid (25 ml) was treated with $KMnO_4$ (0.7 g, 4 mmol) as above to give **31**, yield 0.5 g (77%), colourless granules from hexane, m.p. 140°; MS: (*m/z*): 371 ($M^{+\cdot}$); PMR($CDCl_3$): δ 8.76 (*s*, 1H, H-3), 5.76 (*s*, 2H, N – CH_2O), 4.43-3.6 (*m*, 4H,$CH_2 - CH_2$), 3.3 (*s*, 3H, SO_2CH_3), 2.26 (*s*, 3H, $COCH_3$), 1.9 (*s*, 3H, $COCH_3$) (Found: C, 41.8; H, 4.7' N, 18.5. $C_{13}H_{17}N_5O_6S$ requires C, 42.0; H, 4.6; N, 18.9%).

4-*Amino*-1-(2′-*hydroxyethoxymethyl*)-6-*methoxy-pyrazolo*[3,4-*d*]*pyrimidine* (**33**)

A mixture of **31** (0.5 g, 1.3 mmol), abs. MeOH (40 ml) and MeONa (2 g, 40 mmol) were refluxed for 4 hr. The resulting mixture was worked up as before and the product purified on SiO_2 gel (10 g) column. Elution with EtOAc – MeOH (90:10, v/v) gave **33**, yield 0.22 g (68%), m.p. 208°, MS: *m/z* 239 ($M^{+\cdot}$)); PMR($CDCl_3$ + DMSO-d_6): δ 7.96 (*s*, 1H, H-3), 5.5 (*s*, 2H, N – CH_2 – O), 3.76 (*s*, 4H, $CH_2 - CH_2$), 3.46 (*s*, 3H, OCH_3) (Found: C, 45.2; H, 5.7; N, 28.9. $C_9H_{13}N_5O_3$ requires C, 45.2; H, 5.5; N, 29.2%).

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Antifertility Agents: Part 52—Synthesis & Antiimplantation Study of 4,5-*trans/cis*-1-Acetyl-3,4,5-triarylpyrazolines†‡

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The reaction of 2-phenyl-*p*-methoxyacetophenone (**1**) with benzaldehyde or *p*-hydroxybenzaldehyde gives *E*- and *Z*-isomers of 1,2,3-triarylpropen-1-ones (**2e,z** and **3e,z**). Condensation of the *E*-isomer of **2** (**2e**) and **3e,z** with hydrazine hydrate affords a mixture of 4,5-*trans/cis*-1-acetyl-3,4,5-triarylpyrazolines (**4a,b** and **5a,b**) of which **5a,b** are converted into soluble acetoxy derivatives (**6a,b**). The *trans/cis*-mixtures are separated by column chromatography to give about 90% of *trans*-pyrazolines (**4a** and **6a**) and 10% of *cis*-pyrazolines (**4b** and **6b**). Hydrolysis of *trans*-**6a** gives the *p*-hydroxy derivatives **7** which on alkylation furnishes the β-pyrrolidinoethyl ether **8**. None of these compounds show antiimplantation activity at 20 mg/kg oral dose in female albino rats.

We have studied some di- and tri-aryl(ethanes/ethylenes) and their analogs (I-IV)[1-4] (Chart 1) in an effort to prepare non-steroidal antiestrogenic antiimplantation agents demonstrating less intrinsic estrogenicity. The results reported on related systems V (N≡N-*c*-C_4H_8, trioxifene)[5] and VI (N=N-*c*-C_4H_8, LY-117018 and N=N-*c*-C_5H_{10}, LY-156758)[6] have suggested that spatial placement of three aryl groups can also be set in other fashions without altering the pattern of activity. Further, it is found that *trans*-isomers are more potent[3c,7] antifertility/antiestrogenic agents than the corresponding *cis*-isomers. These observations and the activity exhibited by fused diarylpyrazoles (VII)[8] and *trans*-pyrazolines (I)[1], prompted us to investigate 3,4,5-triarylpyrazolines, a series not studied, so far, for antifertility potential. In this paper, we report the synthesis and antiimplantation activity results of 4,5-*trans/cis*-1-acetyl-3,5-diaryl-4-phenyl-4,5-dihydropyrazoles (VIII).

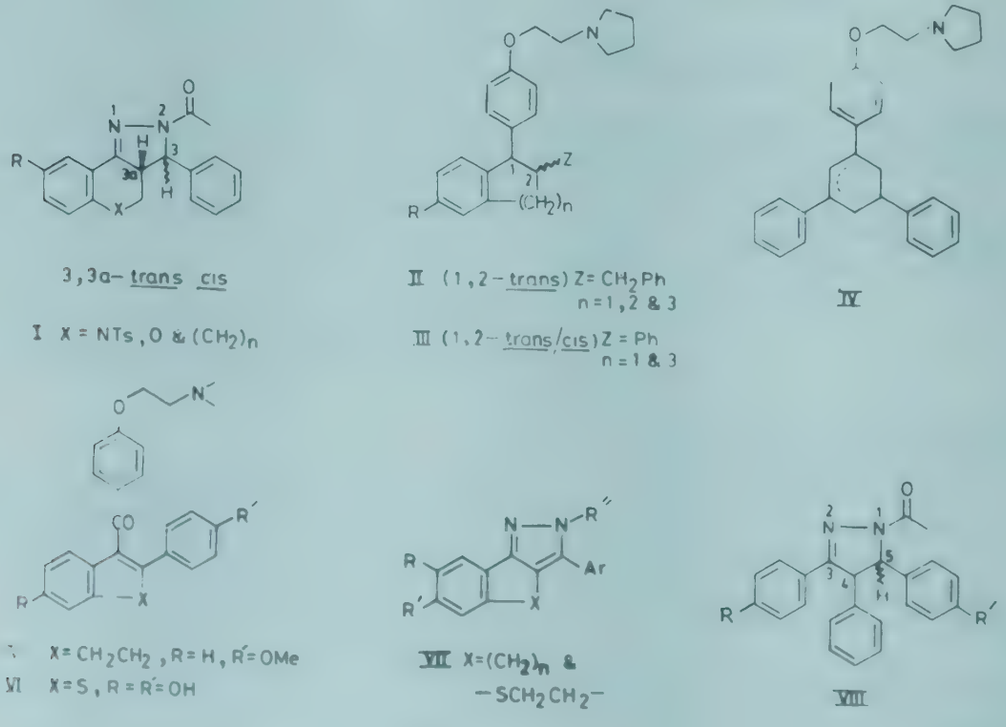
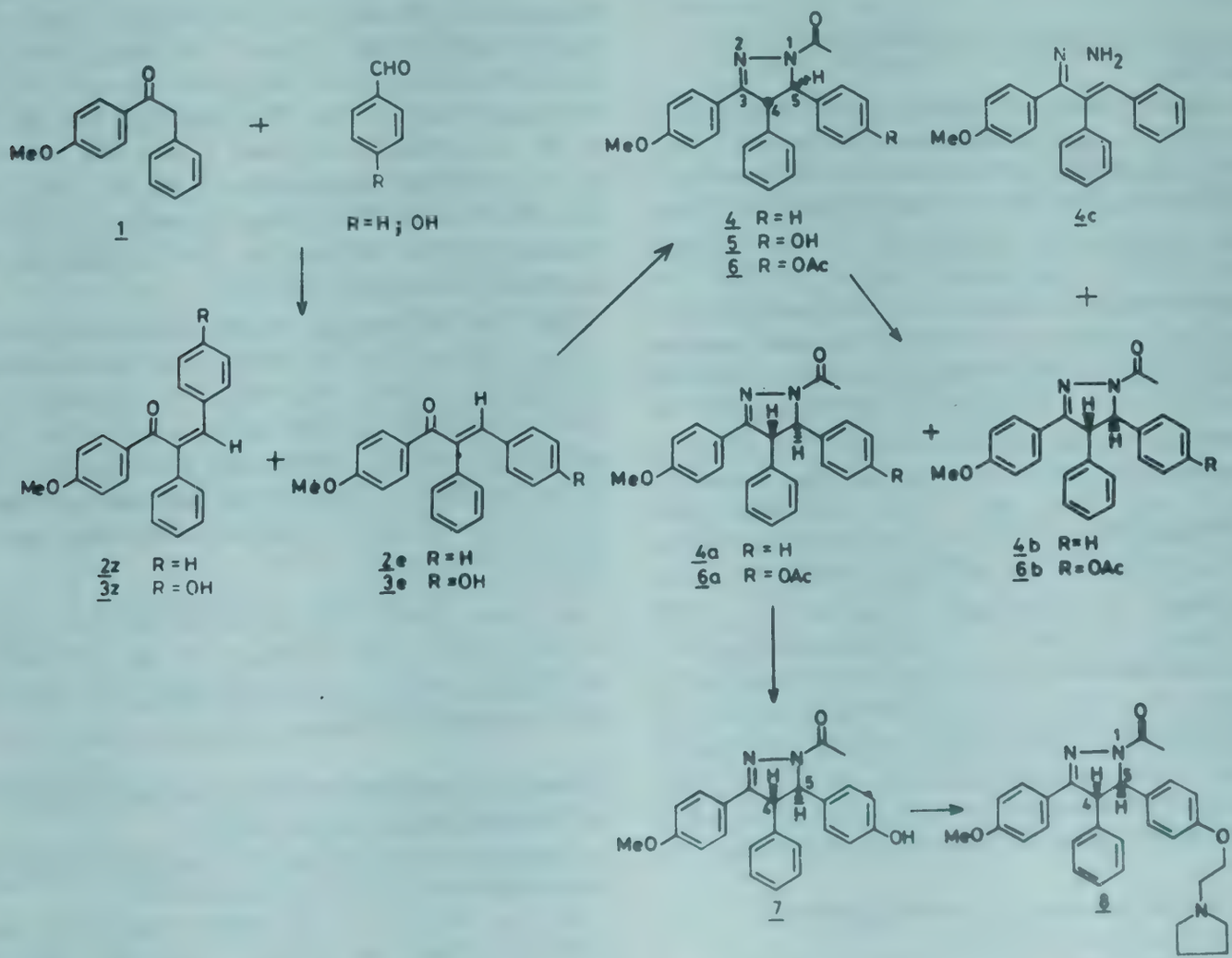

3,3a– trans cis
I X = NTs, O & (CH2)n
II (1,2– trans) Z= CH2Ph n=1,2 & 3
III (1,2– trans/cis) Z = Ph n=1 & 3
IV
V X= CH2CH2, R=H, R'=OMe
VI X=S, R=R'=OH
VII X=(CH2)n & –SCH2CH2–
VIII

Chart 1

†CDRI Communication No. 3976
‡Dedicated to Prof. Charles W Rees, Hofmann Laboratory, Imperial College, London, on his 60th birth anniversary.

The condensation of 2-phenyl-*p*-methoxyacetophenone, prepared by the reaction of phenylacetic acid and anisole, with benzaldehyde or *p*-hydroxybenzaldehyde in the presence of acetic acid and piperidine yielded a mixture of *E*- and *Z*-isomers of 1,2,3-triarylpropen-1-ones (**2e,z** and **3e,z**) (Scheme 1). The *E*- and *Z*-isomers of **2** were separated by column chromatography to give 58% of *E*-isomer (**2e**) and 38% of *Z*-isomer (**2z**). The stereochemical assignment of these was accomplished on the basis of difference in the carbonyl stretching frequency in IR as reported by Duke and Boykins[9]. Thus, the isomer absorbing CO at higher frequency (1665 cm^{-1}) was *Z*-isomer and the other one showing CO at 1640 cm^{-1} was *E*-isomer. The PMR spectra were not of much help in assigning the stereochemistry of these chalcones. The *E*- and *Z*-isomers of **3** could not be resolved due to their insolubility. The reaction of **2e** and **3** with hydrazine hydrate in acetic acid afforded a mixture of 4,5-*trans/cis*-3,4,5-triarylpyrazolines (**4a,b** and **5a,b**) of which **5a,b** were insoluble; in the case of **2e**, a small amount of hydrazone **4c** was also obtained. Treatment of **5a,b** with Ac_2O-pyridine gave a mixture of *trans/cis-p*-acetoxy derivatives (**6a,b**) which were soluble in usual solvents. The *trans/cis*-mixtures of **5a,b** and **6a,b** were separated by silica gel column chromatography using chloroform-benzene as eluant to give 85-90% of *trans*-isomers (**4a** and **6a**) and 10-15% of *cis*-isomers (**4b** and **6b**). The stereochemistry of **4a** and **6a** and of **4b** and **6b** were assigned on the basis of our reported coupling values ($J_{4,5}$) of C_4-H and C_5-H protons in the corresponding *trans/cis*-3,5-diaryl-4,5-dihydropyrazoles[10]. In the PMR spectrum of **4a**, C_4-H and C_5-H appeared as doublets at δ 4.37 (J= 3.5 Hz) and δ 5.3 (J= 3.5 Hz) respectively indictating *trans*-configuration. In **4b** the corresponding C_4-H and C_5-H protons were observed as doublets at δ 5.0 (J= 11.5 Hz) and 5.75 (J= 11.5 Hz) respectively suggesting the 4,5-*cis*-stereochemistry. Similar values were found for **6a** and **6b**. The best purified *cis*-isomers (**4b** and **6b**) were found to contain 10% of *trans*-isomers (**4a** and **6a**) which could not be removed by repeated chromatography. The hydrolysis of **6a** with ethanolic KOH afforded the corresponding *trans-p*-hydroxypyrazoline derivative (**7**) showing C_4-H and C_5-H as doublets in its PMR spectrum at δ 4.35 and 5.15 respectively with J= 3.5 Hz. The alkylation of **7** with N-(β-chloroethyl) pyrrolidine hydrochloride



Scheme 1

in the presence of K_2CO_3 in Me_2CO furnished 4,5-*trans*-1-acetyl-3-(*p*-methoxyphenyl)-4-phenyl-5-[*p*-(β-pyrrolidinoethoxy)phenyl]-4,5-dihydropyrazole (**8**).

Antiimplantation activity

The antiimplantation screening of compounds was carried out by the reported procedure[3a,b]. None of the tested compounds, *trans*-pyrazolines (**4a,6a** and **8**) and *trans/cis*-mixture of pyrazolines (**5** and **4a,b**), showed any antiimplantation activity in a group of 6 albino female rats at 20 mg/kg oral dose.

Experimental Procedure

Melting points were taken in an electrically heated instrument and are uncorrected. Purity of compounds was routinely checked on silica gel G TLC plates. IR spectra (ν_{max} in cm^{-1}) were recorded as neat or in KBr on a Perkin-Elmer 157 spectrometer, PMR spectra on a Perkin-Elmer R-32 (90 MHz) or Varian EM-360L instrument using TMS as internal reference (chemical shifts in δ, ppm) and mass spectra on a Jeol JMS-D300mass spectrometer using a direct inlet system. All the compounds gave elemental analyses within ±0.5% of theoretical values unless otherwise stated.

1-(*p-Methoxyphenyl*)-2,3-*diphenylprop*-2-*en*-1-*ones* (**2e,z**)

A stirred mixture of 2-phenyl-*p*-methoxyacetophenone (**1**) (1.13 g, 5 mmol), benzaldehyde (0.53 g, 5 mmol), piperidine (0.3 ml) and gl. acetic acid (0.1 ml) in dry benzene (30 ml) was refluxed in a Dean-Stark separator till separation of water ceased (about 24 hr). The cooled reaction mixture was washed successively with water (2 × 10 ml) and saturated NaCl solution, dried (Na_2SO_4) and concentrated to dryness to give **2e,z** as a mixture of *E*- and *Z*-isomers, yield 1.26 g (78%). The mixture was resolved by column chromatography over silica gel using benzene as eluant to obtain **2e** (*E*-isomer), yield 0.74 g (58%), m.p. 81-82°; IR (KBr): 1640 (CO); PMR ($CDCl_3$): 3.76 (*s*, 3H, OCH_3), 6.78 (*dd*, 2H, Ar-*H*, *o* to OCH_3, *J*= 9 and 2 Hz), 6.97 (*s*, 1H, Ar-C*H*=C−), 7.05 and 7.21 (two *s*, 10H, 2 × C_6H_5), 7.76 (*dd*, 2H, Ar-*H*, *m* to OCH_3, *J*= 9 and 2 Hz); MS: *m/z* 314 (M^+), 179 ($M^+ - C_8H_7O_2$), 178 ($C_{14}H_{10}$), 135 ($C_8H_7O_2$), 107 (C_7H_7O), 92, 77 (C_6H_5). Further elution of the column gave **2z** (*Z*-isomer), yield 0.47 g (38%), m.p. 78-9°; IR (KBr): 1665 (CO); PMR ($CDCl_3$): 3.52 (*s*, 3H, OCH_3), 6.95 (*s*, 1H, AR-C*H*=C−); MS: *m/z* 314 ($M^{+\cdot}$), etc.

3-(*p-Hydroxyphenyl*)-1-(*p-methoxyphenyl*)-2-*phenylprop*-2-*en*-1-*one* (**3**)

It was prepared as described above for **2e,z. 3**: yield 83%, m.p. 162-64°; IR (KBr): 3400 (OH), around 1645 br (CO); PMR ($CDCl_3$): 2.2 (*h*, 1H, OH, D_2O exchangeable), 3.15 (*s*, 3H, OCH_3), 6.5 (*dd*, 2H, Ar-*H*, *o* to OH, *J*= 9 and 2 Hz), 6.9-7.4 (*m*, 8H, Ar-*H*); MS: *m/z* 330 ($M^{+\cdot}$), 331 ($M^+ + 1$), 236 ($M^+ - C_6H_6O$), 213, 135 ($C_8H_7O_2$), 107 (C_7H_7O), 91 (C_7H_7), 77 (C_6H_5).

4,5-*trans-And cis*-1-*acetyl*-4,5-*diphenyl*-3-(*p-methoxyphenyl*)-4,5-*dihydropyrazoles* (**4a** *and* **4b**) *and* 1-(*p-methoxyphenyl*)-2,3-*diphenylprop*-2-*en*-1-*hydrazone* (**4c**)

A solution of the propenone **2e** (3.1 g, 10 mmol) and hydrazinehydrate (2 ml, slight excess) in gl. acetic acid (20 ml) was refluxed for 8 hr, solvent removed under reduced pressure and the residue treated with water (20 ml) and extracted with EtOAc. The extract ws washed successively with aq. $NaHCO_3$, water and saturated NaCl solution, dried (Na_2SO_4) and concentrated to give **4** as an oil, yield 2.8 g (76%). Column chromatography of the oil over silica gel using chloroform-benzene as eluant gave 85-90% *trans*-isomer (**4a**), 10-15% *cis*-isomer (**4b**) and traces of propenone-hydrazone (**4c**).

4a: m.p. 146-48°; IR (KBr): 1660 ($NCOCH_3$); PMR ($CDCl_3$): 2.47 (*s*, 3H, $NCOCH_3$), 3.66 (*s*, 3H, OCH_3), 4.37 (*d*, 1H, C_4-H, *J*= 3.5 Hz), 5.3 (*d*, 1H, C_5-H, *J*= 3.5 Hz), 6.72 (*dd*, 2H, Ar-H, *o* to OCH_3), *J*= 9 and 2 Hz), 7.2 (*bs*, 10H, Ar-*H*), 7.54 (*dd*, 2H, Ar-*H*, *m* to OCH_3, *J*= 9 and 2 Hz); MS: *m/z* 370 ($M^{+\cdot}$), 328 ($M^+ - 42$), 191 ($C_{14}H_{11}N$), 149, 134, 104, 91 (C_7H_7), 77 (C_6H_5), 65 and 43 ($COCH_3$) (Found: C, 77.6; H, 6.1; N, 7.5. $C_{24}H_{22}N_2O_2$ requires C: 77.8; H, 5.9; N, 7.6%).

4B: Oil; IR (neat); 1660 ($NCOCH_3$); PMR ($CDCl_3$): 2.39 (*s*, 3H, $NCOCH_3$), 3.6 (*s*, 3H, OCH_3), 5.0 (*d*, 1H, C_4-H, *J*= 11.5 Hz), 5.75 (*d*, 1H, C_5-*H*, *J*= 11.5 Hz), 6.7 (*dd*, 2H, Ar-H, *o* to OCH_3, *J*= 9 and 2 Hz), 7.2 (*bs*, 10H, Ar-*H*), 7.45 (*dd*, 1H, Ar-*H*, *m* to OCH_3, *J*= 9 and 2 Hz); MS: *m/z* 370 ($M^{+\cdot}$), 328 ($M^+ - 42$), 191 ($C_{14}H_{11}N$), 149, 134, 104, 91 (C_7H_7), 77 (C_6H_5).

4c: m.p. 204-5°; IR (KBr): 3280 (NH); PMR ($CDCl_3$): 3.65 (*s*, 3H, OCH_3), 6.65 (*dd*, 2H, Ar-*H*, *o* to OCH_3, *J*= 8.5 and 2 Hz), 6.95-7.4 (*m*, 13H, Ar-*H* and Ar-C*H*=C).

1-*Acetyl*-5-(*p-hydroxyphenyl*)-3-(*p-methoxyphenyl*-4-*phenyl*-4,5-*dihydropyrazole* (**5**)

It was prepared by the above method from 3-(*p*-hydroxyphenyl)-1,2-diarylpropenone (**3**).

5: m.p. 196-99° (d); IR (KBr): 3260 (OH), 1645 ($NCOCH_3$); MS: *m/z* 386 (M^+), 344 ($M^+ - 42$), 191 ($C_{14}H_{11}N$), 135, 107 (C_7H_7O), 92, 43 ($COCH_3$)

(Found: C, 75.0; H, 5.3; N, 7.6. $C_{24}H_{22}N_2O_3$ requires C, 74.6; H, 5.7; N, 7.3%).

4,5-*trans*- *And cis*-1-*acetyl*-5-(*p*-*acetoxyphenyl*)-3-(*p*-*methoxyphenyl*)-4-*phenyl*-4,5-*dihydropyrazoles* (**6a,b**)

A solution of **5** (1.0 g, 2.6 mmol) and acetic anhydride (0.33 ml, 3 mmol), in dry pyridine (10 ml) was stirred overnight. The solvent was removed under reduced pressure and the residue treated with water and extracted with EtOAc. The extract was washed successively with water and saturated NaCl solution and dried (Na_2SO_4). Removal of the solvent afforded a mixture of **6a,b** as an oil, yield 0.9 g (81%). The mixture was separated on a silica gel column using benzene as eluant to obtain the major isomer, *trans*-**6a** (about 90%), m.p. 124-26°. Further elution of the column with chloroform furnished the minor isomer, *cis*-**6b** (about 10%) as an oil.

6A: m.p. 124-26°; IR (KBr): 1770 ($OCOCH_3$), 1660 ($NCOCH_3$); PMR ($CDCl_3$): 2.2 (*s*, 3H, $NCOCH_3$), 2.4 (*s*, 3H, $OCOCH_3$), 3.65 (*s*, 3H, OCH_3), 4.4 (*d*, 1H, C_4-H, J= 3.5 Hz), 5.26 (*d*, 1H, C_5-H, J= 3.5 Hz) (Found: C, 73.0; H, 5.9; N, 6.5. $C_{26}H_{24}N_2O_4$ requires C, 73.0; H, 5.6; N, 6.5%).

6b: Oil; IR (neat): 1765 ($OCOCH_3$), 1660 ($NCOCH_3$); PMR ($CDCl_3$): 2.1 (*s*, 3H, $NCOCH_3$), 2.4 (*s*, 3H, $OCOCH_3$), 3.65 (*s*, 3H, OCH_3), 5.0 (*d*, 1H, C_4-H, J= 11.5 Hz), 5.75 (*d*, 1H, C_5-*H*, J= 11.5 Hz); MS: *m/z* 428 ($M^{+\cdot}$).

4,5-*trans*-1-*Acetyl*-5-(*p*-*hydroxyphenyl*)-3-(*p*-*methoxyphenyl*-4-*phenyl*)-4,5-*dihydropyrazole* (**7**)

A suspension of **6a** (0.15 g, 0.35 mmol) in ethanolic KOH (1%, 15 ml) was stirred over night at room temperature. The solvent was distilled off and the residue treated with dil. HCl. The solid was filtered, washed with water and dried to furnish **7**, yield 0.1 g (72%), m.p. 240° (d); IR (KBr): 3400 (OH), 1655 ($NCOCH_3$); PMR ($CDCl_3$): 2.4 (*s*, 3H, $NCOCH_3$), 3.65 (*s*, 3H, OCH_3), 4.0 (*h*, 1H, OH, D_2O exchangeable), 4.35 (*d*, 1H, C_4-H, J= 3.5 Hz), 5.15 (*d*, 1H, C_5-*H*, J= 3.5 Hz) (Found: C, 74.4; H, 5.9; N, 7.3. $C_{24}H_{22}N_2O_3$ requires C, 74.6; H, 5.7; N, 7.3%).

4,5-*trans*-1-*Acetyl*-3-(*p*-*methoxyphenyl*)-4-*phenyl*-5-[*p*-(β-*pyrrolidinoethoxy*)*phenyl*]4,5-*dihydropyrazole* (**8**)

A mixture of **7** (0.1 g, 0.26 mmol), N-(β-chloroethyl)pyrrolidine hydrochloride (0.05 g, 0.29 mmol) and baked K_2CO_3 (0.14 g, 1.0 mmol) in dry acetone (15 ml) was refluxed under stirring for 12 hr. The reaction mixture was filtered and filtrate concentrated. The residue was taken up in ether, washed successively with water and saturated NaCl solution, dried (Na_2SO_4) and concentrated to give **8** as an oil, yield 0.11 g (87%); IR(neat): 1650 ($NCOCH_3$); PMR ($CDCl_3$): 2.35 (*s*, 3H, $NCOCH_3$), 2.3-2.9 [*m*, 6H, $CH_2N(CH_2)_2$], 3.6 (*s*, 3H, OCH_3), 4.0 (*t*, 2H, OCH_2, J= 6 Hz), 4.34 (*d*, 1H, C_4-H, J= 3.5 Hz), 5.2 (*d*, 1H, C_5-H, J= 3.5 Hz); MS: *m/z* 483 ($M^{+\cdot}$), 484 ($M^+ + 1$), 482 ($M^+ - 1$), 385 ($M^+ - C_6H_{12}N$), 343 ($385 - COCH_2$), 250, 135, 98 ($C_6H_{12}N$), 97 ($C_6H_{11}N$), 85 ($C_5H_{11}N$), 84 ($C_5H_{10}N$), 43 ($COCH_3$) (Found: C, 74.6; H, 6.7; N, 8.9. $C_{30}H_{33}N_3O_3$ requires C, 74.5; H, 6.8; N, 8.7%).

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Notes

HOMCOR (COSY) Two Dimensional NMR Spectroscopy in Structure Elucidation of Lignans & in Detection of *cis-trans* Isomerisation

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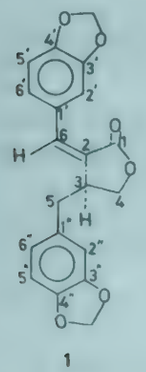
HOMCOR (COSY) 2D NMR spectroscopy have been used in the structure elucidation of gadain (**1**), a new lignan from *Jatropha gossypifolia* Linn and its *trans*-(E)-isomer (**2**).

A new lignan gadain (**1**) was isolated from *Jatropha gossypifolia* Linn (Euphorbiaceae) and its structure was established as *cis*-(*Z*)-2-piperonylidene-3-piperonyl-3*R*-γ-butyrolactone[1]. Subsequently the synthesis of (±)-gadain was also accomplished[2]. While studying the PMR spectrum of **1** in $CDCl_3$ an interesting *cis-trans* isomerisation was observed. Two species, the *cis*-(*Z*)-isomer (**1**) and its *trans*-(*E*)-form (**2**) could be detected. With time **1** changed to **2**. The conversion was not reversible and was possibly catalysed by the usual trace of hydrochloric acid in $CDCl_3$. In fact, on leaving gadain (**1**) in 1 *N* hydrochloric acid for 72 hr at room temperature it changed completely to **2**.



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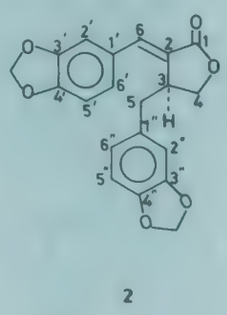

2

We now like to report the complete analysis of the 2D NMR spectral data (Figs. 1 and 2) of the two isomers **1** and **2** and to show how such studies could be utilised in establishing the structures of unknown but related lignan systems. The 2D NMR experiment was carried out using a Varian XL-300 spectrometer (chemical shifts are expressed in δ ppm, downfield from TMS internal reference).

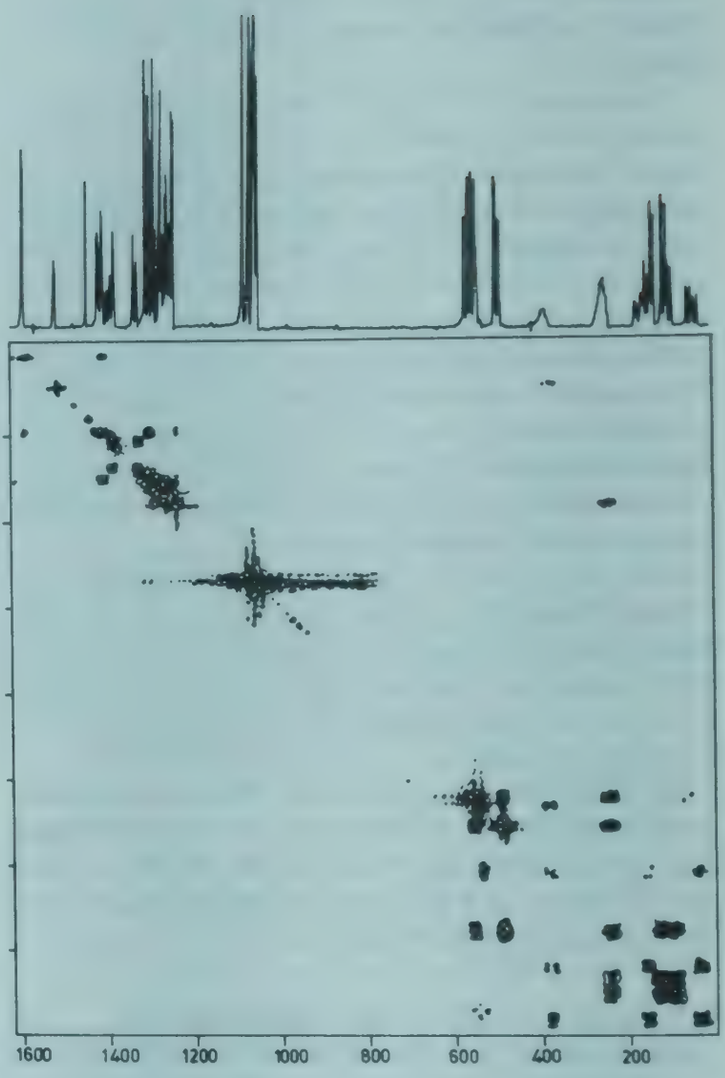

Fig. 1 — HOMCOR (COSY) 2D NMR spectra of gadain (**1**) and its *trans*-(E)-isomer (**2**)

From Figs 1 and 2 it is clearly apparent that there are six aromatic protons in gadain (**1**) which appeared as two ABX patterns. The C_2-H appeared downfield at δ 7.75 (*d*, J = 1.5 Hz) as it was deshielded by the carbonyl group at C-1. This indicated the *cis*-(Z)-configuration of the double bond at the 2,6-position of **1**. The $C_{2'}$-H could be clearly seen to couple with the $C_{6'}$-H at 7.17 (*dd*, J = 8.0 and 1.5 Hz). The latter coupled with the $C_{5'}$-H at 6.80 (*d*, J = 8.0 Hz). The $C_{6''}$-H at 6.77 (*dd*, J = 8.0 and 1.5 Hz) coupled with both the $C_{5''}$-H at 6.66 (*d*, J = 8.0 Hz) and the $C_{2''}$-H at 6.70 (*d*, J = 1.5 Hz). The olefinic proton at C-6 which appeared at 6.59 (*d*, J = 1.6 Hz) showed a long range coupling with the allylic proton at C-3 (3.31, *m*). The latter also coupled with the two protons at C-5 (2.92, *dd*, J = 14.8 and 6.8 Hz and 2.82, *dd*, J = 14.8 and 8.4 Hz). The latter two protons

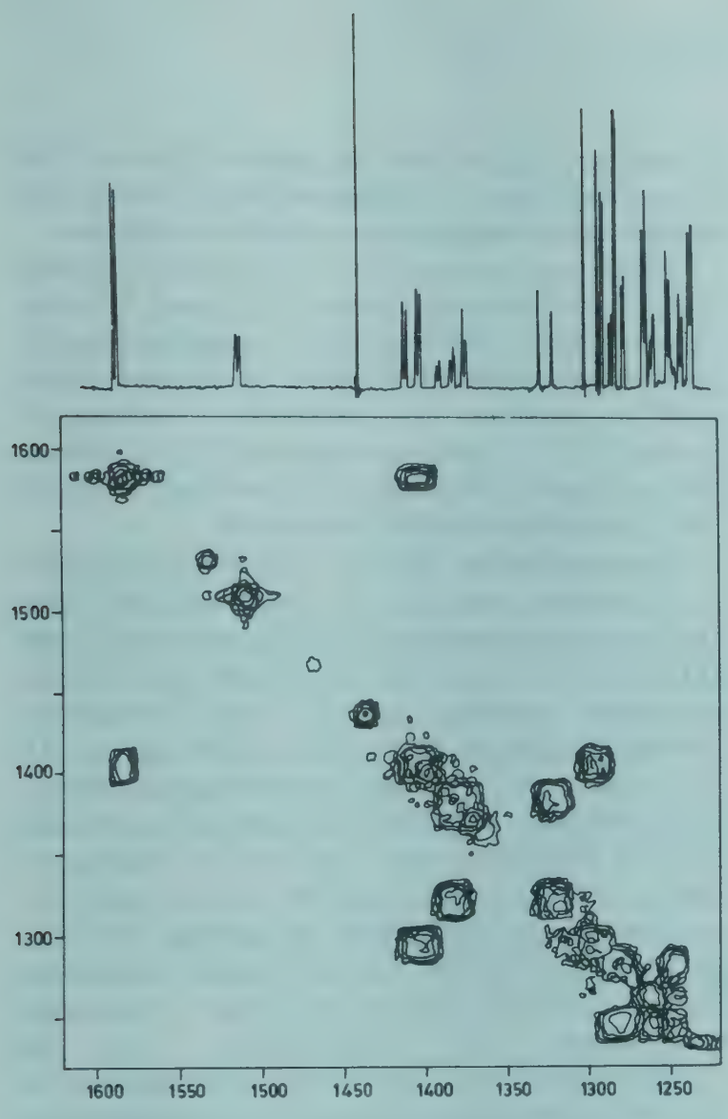

Fig. 2 — HOMCOR (COSY) 2D NMR spectra of gadain (**1**) and its *trans*-(E)-isomer (**2**) (δ 7.75-6.59)

showed a geminal coupling with each other. The proton at C-3 again coupled with the two non-equivalent protons at C-4 (4.34, *dd*, J= 12.8 and 8.4 Hz and δ 4.12, *dd*, J= 12.8 and 4.8 Hz).The couplings between the two non-equivalent protons at C-4 was also evident.

Figures 1 and 2 also clearly show the presence of *trans*-(*E*)-isomer (**2**) in addition to gadain (**1**). The intensity of the signals of **2** were lower compared to that of the corresponding signals of **1**. In the aromatic region **2** showed two ABX patterns. The $C_{6'}$-H at 7.11 (*dd*, J= 8.0 and 1.5 Hz) showed coupling with protons at C-5′ (6.89, *d*, J= 8.0 Hz) and C-2′ (7.07, *d*, J= 1.5 Hz). The $C_{6''}$-H at 6.75 (*dd*, J= 8.0 and 1.5 Hz) coupled with the protons at C-5″ (6.64, J= 8.0 Hz) and C-2″ (6.68, J= 1.5 Hz). The olefinic proton at C-6 appeared downfield at 7.54 (*d*, J= 1.6 Hz) due to the deshielding by the carbonyl group at C-1 and showed an allylic coupling with the C_3-H (3.72, *m*). This suggested the *trans*-(E)-configuration of the double bond at the 2,6-position of **2**. The C_3-H also coupled with the two non-equivalent protons at C-4 (4.32-4.24, *m*) and with other two non-equivalent protons at C-5 (δ 3.02, *dd*, J= 14.8 and 4.8 Hz and 2.60, *dd*, J= 14.8 and 8.4 Hz). Carbon connecting relationships could thus be established from the HOMCOR (COSY) 2D NMR spectra of gadain (**1**) and its *trans*-(E)-isomer (**2**).

The spectra clearly indicated the upfield shift of the aromatic proton at C-2′ by 0.68 ppm (from 7.75 to 7.07) and the downfield shift of the olefinic proton at C-6 by 0.95 ppm (from 6.59 to 7.54). This is associated with the fact that in **1** the $C_{2'}$-H is deshielded by the carbonyl group at C-1 confirming the presence of *cis*-(Z)-double bond in **1** while in its isomer **2** the C_6-H is deshielded by the carbonyl group at C-1 confirming the presence of *trans*-(E)-double bond in **2**. This type of isomerisation is also expected for other monoarylidenebutyrolactone lignans and warrants detailed reinvestigation of some of the earlier structures.

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A Convenient Synthesis of 2-Styrylchromones by the Modified Baker-Venkataraman Transformation

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The condensation of *o*-hydroxyacetophenones (Ia-f) with cinnamoyl chloride in acetone-K_2CO_3 medium involves the modified Baker-Venkataraman transformation to give 7-cinnamoyloxy- or 5,7-dicinnamoyloxy-3-substituted-2-styrylchromones (II). The 7-cinnamoyloxy(IIb,c)- and 5,7-dicinnamoyloxy(IIe,f)-2-styrylchromones on hydrolysis with methanolic KOH furnish the corresponding 7-hydroxy(IIIb,c) or 5,7-dihydroxy(IIIe,f) derivatives. However, the 7-cinnamoyloxy(IIa)- and 5,7-dicinnamoyloxy(IId)-2-styrylchromones on a similar hydrolysis do not give the corresponding 7-hydroxy(IIIa)- and 5,7-dihydroxy(IIId)-2-styrylchromones as in these cases the chromone ring undergoes decomposition. The hydroxystyrylchromones (IIIb,c,e and f) have been methylated with dimethyl sulphate in acetone-K_2CO_3 medium to furnish the methoxystyrylchromones (IVb,c,e and f).

The conventional Baker-Venkataraman transformation for the synthesis of 2-phenylchromones involves a number of steps[1,2]. However, the modified Baker-Venkataraman transformation[3-7] yields the 2-phenylchromones in a single step. This modified transformation has now been applied for the synthesis of 2-styrylchromones in high yields. Earlier, 2-styrylchromones were synthesized by the Kostanecki method[8,9] involving the condensation of *o*-hydroxyacetophenones with cinnamoyl chloride in toluene-K_2CO_3, and also by the condensation of 2-methylchromones with aromatic aldehydes[10,11]. All these reactions required a higher reaction temperature, involved a number of intermediate steps and the yields were also poor.

In the present study condensation of resacetophenone[12] (Ia), respropiophenone (Ib)[13], 2,4-dihydroxyphenyl benzyl ketone (Ic)[14], phloroacetophenone (Id)[13], phloropropiophenone (Ie)[13] and 2,4,6-trihydroxyphenyl benzyl ketone (If)[14] with cinnamoyl chloride in refluxing acetone containing anhyd. K_2CO_3 afforded 7-cinnamoyloxy (IIa-c) or 5,7-dicinnamoyloxy (IId-f)-2-styrylchromones in high yields (~85%). The crude cinnamoyloxy-2-styrylchromones (IIb,c,e and f) were hydrolysed with 5% methanolic KOH to give the corresponding hydroxy-2-styrylchromones (IIIb,c,e and f) in about 85% yield. However, the hydrolysis of 7-cinnamoyloxy(IIa)- and 5,7-dicinnamoyloxy(IId)-2-styrylchromones did not yield the expected IIIa and IIId respectively since the chromone ring in these cases underwent decomposition on alkaline hydrolysis.

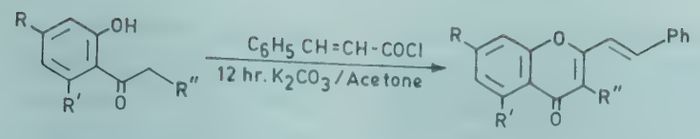
7-Hydroxy-3-methyl(IIIb)-, 7-hydroxy-3-phenyl (IIIe)-, 5,7-dihydroxy-3-methyl (IIIe)- and 5,7-dihydroxy-3-phenyl(IIIf)-2-styrylchromones were methylated with dimethyl sulphate in acetone-anhyd. K_2CO_3 medium to furnish 7-methoxy-3-methyl(IVb)-, 7-methoxy-3-phenyl(IVc)-, 5,7-dimethoxy-3-methyl(IVe)- and 5,7-dimethoxy-3-phenyl (IVf)-2-styrylchromones, respectively.

Although IIa, IIb, IIIb, IIIe, IIIf, IVb, IVc and IVf were earlier synthesized by other methods, their spectra were not recorded. The IR spectra of IIa and IId showed two carbonyl absorptions at 1735 (cinnamoyloxy carbonyl) and 1625 cm^{-1} (chromone carbonyl) and those of hydroxystyrylchromones (IIIb,c,e and f) and methoxystyrylchromones (IVb,c,e and f) exhibited a characteristic chromone carbonyl band at 1620-1630 cm^{-1}. In the UV (methanol) spectra of IIIb,c,e and f and IVb,c,e and f three absorption bands appeared in the regions 206-208, 260-280 and 335-346 nm. The longer wavelength band at 335-346 nm, which is due to extended conjugation, is characteristic of the $-CH-CH=CH-CH=CH$-Ph chromophore. In the PMR spectra, the α-styryl proton resonated as a doublet around δ 6.80 while the β-styryl proton resonated as a doublet around 7.60 with $J = 16.0$ Hz, indicating their *trans*-orientation. In the mass spectra of IIIb,c,d,f and IVb,c,d,f intense peaks appeared due to $M^{+\cdot}$, $M-1$, $M-CO$, $M-Ph$ and retro Diels-Alder fragmentation ions V and VI. In the 3-methyl-2-styrylchromones IIIb and IIIe, an intense peak appeared at *m/z* 141 which was due to the ion VII.

Melting points were determined in a sulphuric acid-bath and are uncorrected. IR (KBr) spectra were recorded on a Perkin-Elmer infracord 337 spectrophotometer (ν_{max} in cm^{-1}), UV (methanol) spectra on a Shimadzu UV-VIS 200 spectrophotometer (λ_{max} in nm, log ε in parentheses), PMR ($CDCl_3$) spectra on a Varian A60D instrument with TMS as internal standard (chemical shifts in δ, ppm), and mass spectra on a Perkin-Elmer Hitachi RMU-6L mass spectrometer.

7-*Hydroxy- and* 5,7-*dihydroxy*-2-*styrylchromones* (*IIIa-f*)

A solution of I (10 mmol) and cinnamoyl chloride (20 mmol) (30 mmol in the case of Id-f) was refluxed



Ia R=OH, R′, R″=H
b R=OH R′=H R″=CH3
c R=OH R′=H R″=Ph
d R, R′=OH R″=H
e R, R′=OH, R″=CH3
f R, R=OH, R″=Ph

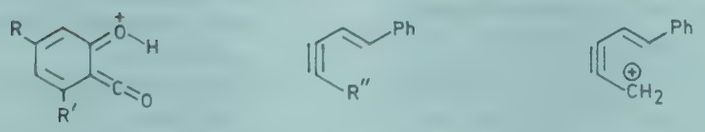
IIa R=O-C(=O)-CH=CH-Ph, R′, R″=H
•b R=O-C(=O)-CH=CH-Ph, R′=H, R″=CH3
•c R=O-C(=O)-CH=CH-Ph, R′=H, R″=Ph
d R, R′=OC(=O)-CH=CH-Ph, R″=H
•e R, R′=OC(=O)-CH=CH-Ph, R″=CH3
•f R, R′=OC(=O)-CH=CH-Ph, R″=Ph

IIIa•• R=OH, R′, R″=H
b R=OH, R′=H, R″=CH
c R=OH, R′=H, R″=Ph
••d R, R′=OH, R″=H
e R, R′=OH, R″=CH3
f R, R′=OH, R″=Ph

IV b R=OCH3, R′=H R″=CH3
c R=OCH3, R′=H R″=Ph
e R, R′=OCH3 R″=CH3
f R, R′=OCH3, R″=Ph

• II b,c,e,f were not isolated

••III a,d chromone ring decomposed in alcoholic alkali 5%



(V) (VI) (VII)

with anhyd. K_2CO_3 (10 g) in acetone (200 ml) for 12 hr on a water-bath, acetone removed under reduced pressure and the residue treated with cold water to give a yellow product. The crude cinnamoyloxy-styrylchromones (IIa-f) thus obtained were hydrolysed with 5% methanolic KOH (100 ml) under reflux for 1/2 hr on a water-bath. The alcohol was removed under reduced pressure and the residue suspended in chilled water and acidified with dil. HCl. The crude product was filtered and washed with sodium bicarbonate to remove cinnamic acid to yield IIIb, IIIc, IIIe or IIIf. The compounds IIIa and IIId could not be obtained from IIa and IId respectively since the chromone ring in these cases underwent decomposition in alkali. Therefore IIa and IId were crystallized and characterised as given below:

7-Cinnamoyloxy-2-styrylchromone (IIa): Crystallised from acetic acid as pale yellow needles, yield 85%, m.p. 216° (lit[2]., m.p. 216-17°); IR: 1735 and 1625 (C=O).

5,7-Dicinnamoyloxy-2-styrylchromone(IId): Crystallised from acetic acid as yellow needles, yield 85%, m.p. 235° (lit[8]., m.p. 235°); IR: 1735 and 1625 (C=O).

The characterization data of III are as follows:

7-Hydroxy-3-methyl-2-styrylchromone(IIIb): Crystallised from acetone as pale yellow needles, yield 85%, m.p. 307° (lit[8]., m.p. 307°); IR: 1625 (C=O); UV: 208 (4.20), 220 sh (4.02), 232 (4.12), 262 (inf; 3.10) and 340 (4.38); PMR: 6.87 (1H, *d*, J=16.0 Hz, styryl α-H), 7.67 (1H, *d*, J=16.0 Hz, styryl β-H), 7.79-6.80 (8H, *m*, Ar-*H*), 2.15 (3H, *s*, C_3-CH_3); MS: *m/z* 278 ($M^{+\cdot}$), 277, 263, 201, 141 and 137.

7-Hydroxy-3-phenyl-2-styrylchromone(IIIc): Crystallised from methanol as pale yellow feathery solid, yield 80%, m.p. 297° (lit[9]., mp. 298°); IR: 1620 (C=O); UV: 208 (4.14), 236 inf (3.93), 266 (3.70) and 346 (4.16); PMR: 6.69 (1H, *d*, J=16.0 Hz, styryl α-H), 7.68 (1H, *d*, J=16.0 Hz, styryl β-H), 6.87 (1H, *d*, J=1.5 Hz, C_6-H), 6.99 (1H, *d*, J=1.5 Hz, C_8-H), 7.90 (1H, *d*, J=9.0 Hz, C_5-H), 7.4 (10H, *m*, Ar-*H*); MS: *m/z* 340 ($M^{+\cdot}$) 339, 263, 204 and 137.

5,7-Dihydroxy- 3-methyl-2-styrylchromone (IIIe): Crystallised from methanol as yellow flakes, yield 85%, m.p. 260° (Found: C, 73.5; H, 4.8. $C_{18}H_{14}O_4$ requires C, 73.47; H, 4.76); IR: 1620 (C=O); UV: 208 (4.36), 212 (4.37), 260 inf (3.97),

280 (4.14) and 336 (4.35); PMR: 8.12-6.70 (7H, *m*, styryl α- and β-H and Ar-*H*), 6.1 (1H, *d*, J = 1.5 Hz, C_6-H); 6.40 (1H, *d*, J = 1.5 Hz, C_8-H), 2.12 (3H, *s*, C_3-CH_3); MS: *m/z* 294 ($M^{+\cdot}$) 293, 279, 217, 153 and 141.

5,7-Dihydroxy-3-phenyl-2-styrylchromone(IIIf): Crystallised from ethanol as yellow rods, yield 80%, m.p. 281° (lit[9]., m.p. 281°); IR: 1625 (C=O); UV: 206 (4.23), 214 sh (4.16), 230 (4.12), 284 (4.17) and 334 (4.20); PMR: 6.40 (1H, *d*, J = 16 Hz, styryl α-H), 6.20-7.80 (13H, *m*, styryl β-H and Ar-*H*); MS: *m/z* 346 ($M^{+\cdot}$) 355, 279, 204 and 153.

7-Methoxy- and 5,7-dimethoxy-2-styrylchromones (IVb, IVc, IVe and IVf)

To a solution of IIIb, IIIc, IIIe or IIIf (10 mmol) in acetone (100 ml) anhyd. K_2CO_3 (5 g) and dimethyl sulphate (25 mmol) were added and the mixture was refluxed for 6 hr (for IIIb and IIIc) or 20 hr (for IIIe and IIIf). Potassium carbonate was then filtered off, the solution evaporated and the residue treated with cold water when IVb, IVc, IVe or IVf separated out. Their characterization data are given below:

7-Methoxy-3-methyl-2-styrylchromone (IVb): Crystallised from methanol as colourless needles, yield 95%, m.p. 152° (lit.[16], m.p. 152°); IR: 1625 (C=O); UV: 208 (4.14), 234 (3.97), 266 (3.50) and 340 (4.24); PMR: 6.85 (1H, *d*, J = 16.0 Hz, styryl α-H), 7.60 (1H, *d*, J = 16.0 Hz, styryl β-H), 7.78-6.80 (8H, *m*, Ar-*H*), 3.90 (3H, *s*, C_7-OCH_3), 2.15 (3H, *s*, C_3-CH_3); MS: *m/z* 292 ($M^{+\cdot}$) 291, 277, 215, 151 and 141.

7-Methoxy-3-phenyl-2-styrylchromone (IVc): Crystallised from methanol as colourless needles, yield 95%, m.p. 204° (lit.[15], m.p. 203-204°); IR: 1625 (C=O); UV: 208 (4.25), 235 (3.99), 266 (3.72) and 3.44 (4.19); PMR: 6.80 (1H, *d*, J = 16.0 Hz, styryl α-H), 7.60 (1H, *d*, J = 16.0 Hz, styryl β-H), 8.14 (1H, *d*, J = 9.0 Hz, C_5-H), 7.42-6.19 (12H, *m*, Ar-*H*), 3.94 (3H, *s*, C_7-OCH_3); MS: *m/z* 354 ($M^{+\cdot}$) 353, 277.

5,7-Dimethoxy-3-methyl-2-styrylchromone (IVe): Crystallised from methanol as light yellow needles, yield 95%, m.p. 175° (Found: C, 74.6; H, 5.6. $C_{20}H_{18}O_4$ requires C, 74.53; H, 5.59; IR: 1630 (C=O); UV: 208 (4.46), 214 sh (4.45), 272 (4.16) and 340 (4.48); PMR: 7.05 (1H, *d*, J = 16.0 Hz, styryl α-H), 7.51 (1H, *d*, J = 16.0 H, styryl β-H), 6.31 (1H, *d*, J = 2.0 Hz, C_6-H), 6.48 (1H, *d*, J = 2.0 Hz, C_8-H), 7.53-7.25 (5H, *m*, Ar-*H*), 3.90 and 3.97 (each 3H, *s*, C_5- and C_7-OCH_3), 2.15 (3H, *s*, C_3-CH_3); MS: *m/z* 322 ($M^{+\cdot}$) 321, 245.

5,7-Dimethoxy-3-phenyl-2-styrylchromone (IVf): Crystallised from methanol as pale yellow flakes, yield 95%, m.p. 230° (lit.[11], m.p. 230°); IR: 1625 (C=O); UV: 206 (4.46), 228 (4.25); 276 (4.20) and 344 (4.35); PMR: 6.13-7.73 (14H, *m*, styryl α- and β-H and Ar-*H*), 3.83 (6H, *s*, C_5- and C_7-OCH_3); MS: *m/z* 384 ($M^{+\cdot}$) and 383.

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Novel Dimeric Compounds in Reaction of Benzofuran Derivatives with Phosphoric Acid†

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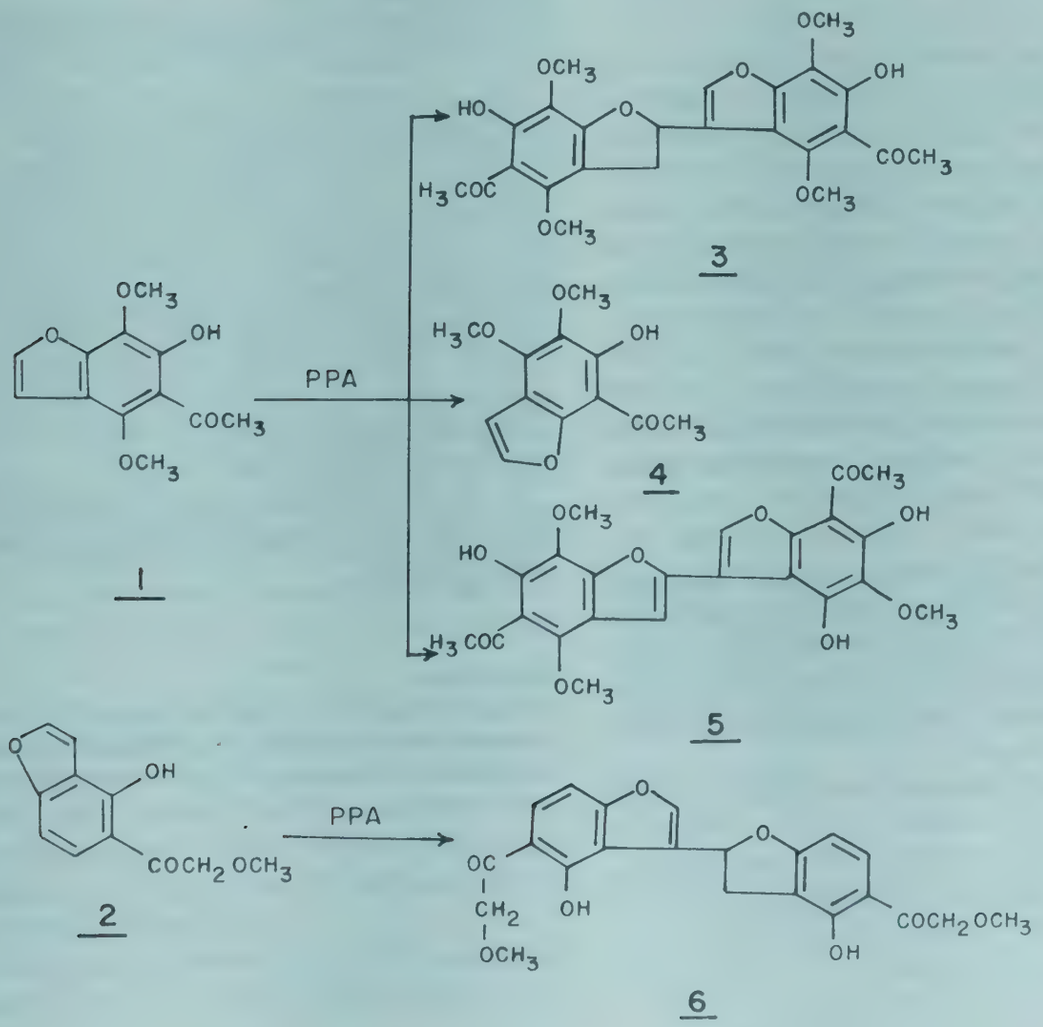
Novel dimeric compounds **3, 5** and **6** have been obtained on treatment of benzofuran derivatives, kellinone (**1**) and karanj ketone (**2**) with polyphosphoric acid. The products have been characterized with the help of their spectral data.

Reaction of benzofuran derivatives in the presence of acid reagents generally leads to cationic polymerisation. However, presence of other substituents in the nucleus may modify this. In an attempt to prepare certain benzofuran derivatives from hydroxyphenylacetaldehyde precursors, the use of polyphosphoric acid (PPA) as a cyclising agent led to the formation of novel dimeric self-condensation products, the structure elucidation of which forms the subject of the present note.

Kellinone (**1**) on keeping with PPA (prepared from phosphorus pentoxide, 0.5 g and orthophosphoric acid, 0.5 ml) at 70° for 2 hr under moisture-free conditions gave three products, **3, 4** and **5**, separated by column chromatography over silica gel.

Product **3** crystallised as pale yellow needles from ethanol, m.p. 185° (Found: C, 60.4; H, 5.0. $C_{24}H_{24}O_{10}$ requires C, 61.0; H, 5.1%); MS: *m/z* 472 (M^+). It showed following spectral characteristics: UV (MeOH): 256, 288 nm; IR ($CHCl_3$): 1650, 1600, 1395, 1350, 1265, 1070, 960 cm^{-1}. Its PMR spectrum in $CDCl_3$ displayed a two-proton doublet (J=8 Hz) at δ 3.93 and a one-proton multiplet at 4.77 assignable to methylene protons that resulted by the hydrogenation of the double bond of furan ring during reaction. The carbonium ion generated



1 2 3 4 5 6

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by deprotonation of one of the furan rings at α-position perhaps undergoes condensation with a second molecule of furan at β-position to form a dimer. The other PMR peaks at 2.50 (3H), 2.56 (3H) due to two acetyl groups; 3.7 (6H), 3.8 (6H) due to four methoxyls and a broad one-proton singlet at 6.37 due to one proton on one of the furan rings unambiguously support structure (**3**) for the symmetrical dimer formed from two molecules of kellinone (**1**), similar to acid-catalysed dimerisation of benzofuran derivatives reported earlier by Abe and Shimizo[1].

Product **4** obtained as yellow needles from ethanol, m.p. 112° (Found: C, 61.2; H, 5.0. $C_{12}H_{12}O_5$ requires C, 61.0; H, 5.1%); UV (MeOH): 255, 344 nm; IR ($CHCl_3$): 3490, 1650, 1600, 1235, 1080, 1015, 805 cm^{-}; MS: *m/z* 236 (M^+), appeared isomeric with parent **1**. Its PMR spectrum ($CDCl_3$) was almost similar to that of **1**, except that one of the methoxyl groups appearing at δ 4.04 in **1** shifted to 4.13 in product **4** and H-β shifted from 6.87 in **1** to 6.37 in **4**. A ketone with similar structure and very close m.p. (110°) has been prepared earlier by Horton and Stout[2] during the synthesis of allokellin from antriol.

The formation of product **4** by isomerisation of kellinone (**1**) is intriguing. Apparently it involves demethylation of the methoxyl group at position-4 of **1**, furan ring-opening and reclosing with the free hydroxyl group at position-4 followed by remethylation of the free hydroxyl group. formed by the cleavage of furan ring. Although such isomerisations involving opening and reclosing of the furan ring under acid-catalysed conditions are known[2,3] but remethylation in these cases involved the use of such reagents as CH_3I. In the present case the formation of 4,6-dihydroxy-5-methoxy-7-acetylbenzofuran would not have been surprising but the actual product isolated is the methyl ether (**4**). One may suggest that the methylating reagent in the present case is the methyl ester of PPA formed by the action of methyl radical with PPA during the demethylation of **1**. In contrast the methyl iodide formed during demethylation by hydroiodic acid[2,3] probably escaped, being a low boiling liquid.

Compound **5** was obtained as an intense yellow prismatic solid, m.p. 120° (Found: C, 60.0; H, 4.8. $C_{23}H_{20}O_{10}$ requires C, 60.5; H, 4.4%); MS: *m/z* 454 (M-2). The analytical and mass data indicated it to be a dimer. Its IR spectrum in $CHCl_3$ [1640, 1600, 1430, 1385, 1270, 1120, 1070, 920, 840 cm^{-1}] was very similar to that of **1** except for some differences only in the finger print region. Its PMR spectrum in $CDCl_3$ [two 3-proton singlets at δ 2.40 and 2.60 of two acetyl groups in place of one at 2.50 (3H) in 1, two singlets at 4.13 (3H) and 3.90 (6H) in place of two 3-proton sinlgets each at 4.04 and 3.87 for **1**; and 7.63 and 6.47 for one proton each of α- and β-protons of furan ring] indicated it to be an asymmetrical dimer. Integration of peaks at 7.63 and 6.47 for one proton each and intensity of maximum absorption at 295 nm in its UV spectrum in CH_3OH reveals continuous conjugation in the dimer. It appears that the dimer is formed by the condensation of one mol of kellinone (**1**) and one mol of isomerised and demethylated kellinone. The dimer formed undergoes further benzylic oxidation to produce a double bond in the furan ring. Structure **5** can thus be assigned to this asymmetrical dimer on the basis of above data.

Karanj ketone (**2**) gave only one product as a yellowish solid, m.p. 160° (Found: C, 64.0; H, 5.0. $C_{22}H_{20}O_8$ requires C, 64.1; H, 4.9%); MS: *m/z* 412 (M^+); PMR ($CDCl_3$): δ 4.27 (*d*, *J*=7 Hz, 2H, furan 3-CH_2), 4.93 (*t*, *J*=6 Hz, furan 2-CH), 3.55, 3.58 (each *s*, each 3H, 2 × OCH_3); 4.70, 4.78 (each *s*, 2H each, 2 × $COCH_2$); 6.71 (*d*, *J*=9 Hz, 1H, Ar-H), 6.87 (*d*, *J*=9 Hz, 1H, Ar-H), 7.33 (*s*, 1H, furan H), 7.66 (*d*, *J*=8 Hz, 2H, Ar-H); UV (MeOH): 245, 282 nm; IR ($CHCl_3$): 3520; 2920, 2860, 1710, 1640, 1595, 1450, 1375, 1270, 1125, 1070, 950 cm^{-1}. These spectral and analytical data are in agreement with structure (**6**) for the product.

A related furanoketone, visnaginone however gave only red polymeric material on similar treatment with PPA.

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Synthesis of 4-Aryl-3-benzylidenenaphtho[2,3-*c*]furan-1(3*H*)-ones & Related Compounds

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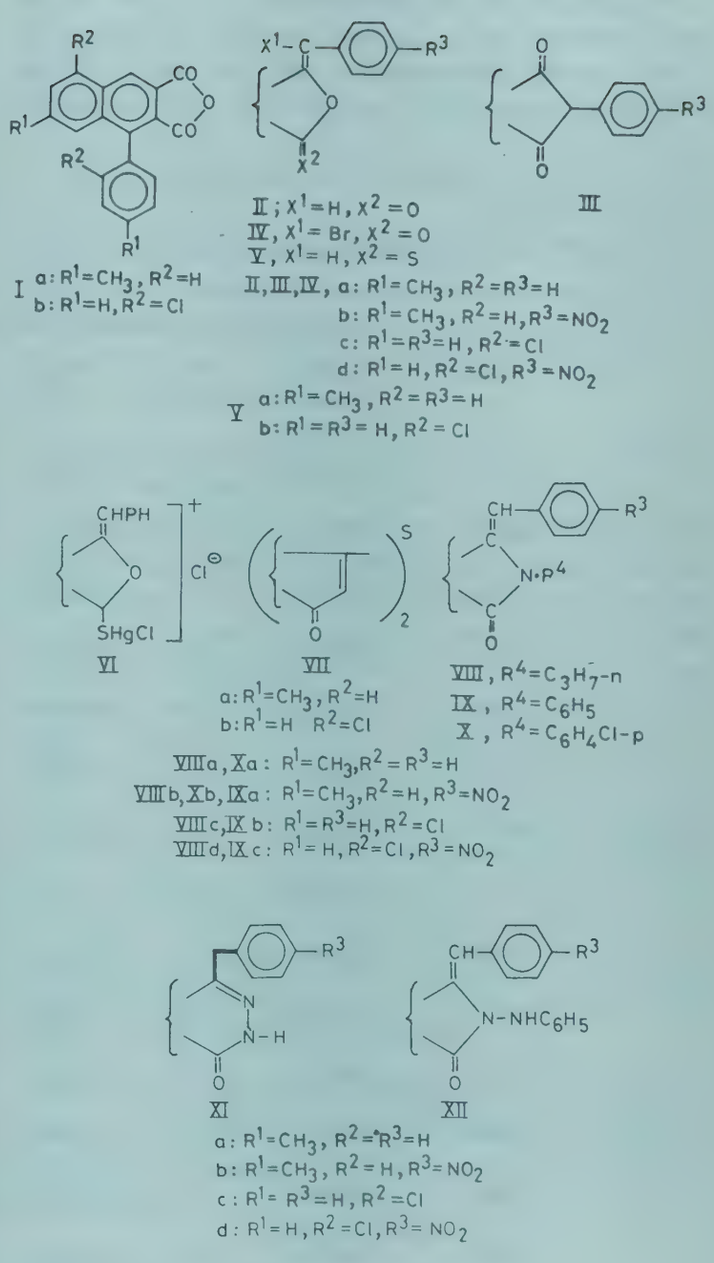
A number of 4-aryl-3-benzylidenenaphtho[2,3-*c*]furan-1(3*H*)-ones (II) have been prepared. These compounds underwent facile rearrangement with sodium methoxide to give 2-arylbenz[*f*]indane -1,3-diones (III). Treatment of II with phosphorous pentasulphide, amines and hydrazine hydrate gives the thiones (V), naphthalimidines (VIII - X) and benzylnaphthalazones (XI), respectively.

In view of the importance of some benzylidenephthalimidines as stabilizers for halogen containing high polymers[1,2] and their local anesthetic activity superior to that of procaine[3], it became desirable to prepare some new benzylidenephthalides and related compounds.

The 4-aryl-3-benzylidenenaphtho[2,3-*c*]furan-1(3*H*)-ones (II) were prepared by condensing 1-phenylnaphthalene-2,3-dicarboxylic anhydrides (Ia,b)[4] with phenylacetic acid and *p*-nitrophenylacetic acid under fusion in the presence of fused sodium acetate. The possibility of formation of the other isomer in each case was ruled out due to steric hindrance as observed by earlier workers[5–7]. Rearrangement of these benzylidenes in sodium methoxide solution gave the corresponding 2-arylbenz[*f*]indan-1,3-diones (III). Treatment of IIa,b with bromine in chloroform afforded the corresponding α-bromo derivatives (V). The benzylidenes IIa,c on reaction with phosphorous pentasulphide in xylene furnished 4-aryl-3-benzylidenenaphtho[2,3-*c*]furan-1(3*H*)-thiones (V).

Fusion of IIa-d with different amines in the presence of fused sodium acetate gave the corresponding naphthalimidines (VIII-X). However, these compounds (II) when reacted with hydrazine hydrate and phenylhydrazine in ethanol afforded the 4-benzylnaphthalazones (XIa-d) and N-anilinonaphthalimidines (XIIa-d), respectively.

The structural assignments of II - XII were based on elemental analyses and characteristic IR and PMR data.



Biological activity

Some of the compounds were tested against the different types of gram - positive and gram - negative bacteria (*Bacillus subtilis, Staphylococcus aureus, Eschericia coli & Pseudimonas aeruginosa*) and unicellular fungi in yeast (*Candida lipolytica*) by the filter paper disc method[8] at 1×10^3 μg/ml concentration in acetone.

The results indicate that 8-chloro-4-(*o*-chlorophenyl)-2-phenylbenz[*f*]indan-1,3-dione (II-Ic) shows the highest activity against *Bacillus subtilis, Staphylococcus aureus* (+ + + +) and *Candida lipolytica* (+ + +) whereas the benzylidene derivative IId, α-bromo derivatives (IVc-d) and 4-benzylnaphthalazone XIc exhibit higher activity against *Bacillus subtilis* (+ + +) than compounds IVb and IXa which exhibit fairly good activity (+ +). The

compounds Vb, IXc, XId and XIId show marginal activity (+) while other compounds are inactive (−).

Melting points are uncorrected. IR (KBr; ν_{max} in cm^{-1}) spectra were recorded on a Pye - Unicam Sp - 1200 spectrophotometer and 60 MHz PMR ($CDCl_3$; δ, ppm) spectra on an EM 360 instrument.

4-Aryl-3-benzylidenenaphtho[2,3-c]furan-1(3H)-ones (II; Table 1)

A mixture of I (0.05 mol), phenylacetic acid (0.05 mol) and freshly fused sodium acetate (0.2 g) was fused in an oil - bath for 1 hr at 200 - 220°. The reaction mixture was cooled, treated with Na_2CO_3 solution (5 %) and the resultant solid recrystallised from an appropriate solvent. In the case of Ia, the product was recrystallised from acetic acid to give 3-benzylidene-6-methyl-4-(*p*-tolyl)-naphtho[2,3-*c*]furan-1(3*H*)-one (IIa) as yellow crystals, yield 80 %, m.p. 189 - 90°; IR : 1790 - 1775 (C = O); PMR: 6.6 (*s*, 1H, olifinic proton of the benzylidene moiety), 7.45 - 8.28 (*m*, 13H, Ar - *H*), 2.55 (*s*, 3H, *p* - tolyl CH_3)

Table 1—Physical Data of the Various Compounds Prepared

Compd.	Crystallized from	Yield (%)	m.p. °C	Mol. formula	Found(%) (Calc.)		
					C	H	N
IIb	AcOH	82	252-55	$C_{27}H_{19}NO_4$	76.5	4.2	3.3
					(77.0	4.5	3.3)
IIc	EtOH	79	220-21	$C_{25}H_{14}Cl_2O_2$	71.9	3.4	—
					(71.9	3.4	—)
IId	AcOH	70	235-36	$C_{25}H_{13}Cl_2NO_4$	65.0	2.3	3.1
					(64.9	2.8	3.0)
IIIb	EtOH	69	261-62	$C_{27}H_{19}NO_4$	76.6	4.2	3.1
					(77.0	4.5	3.3)
IIIc	EtOH	70	129-30	$C_{25}H_{14}Cl_2O_2$	72.0	3.4	—
					(71.9	3.4	—)
IIId	EtOH	82	251-52	$C_{25}H_{13}Cl_2NO_4$	64.9	3.0	3.0
					(64.6	2.8	3.0)
IVb	AcOH	73	175-76	$C_{27}H_{18}BrNO_4$	65.0	3.7	—
					(64.8	3.6	—)
IVc	EtOH	64	207-8	$C_{25}H_{13}BrCl_2O_2$	60.5	2.6	—
					(60.5	2.6	—)
IVd	EtOH	75	225-26	$C_{25}H_{12}BrCl_2NO_3$	70.2	2.9	—
					(70.2	2.8	—)
Vb	AcOH	56	214-15	$C_{25}H_{15}Cl_2OS$	69.1	3.2	—
					(69.3	3.2	—)
VIIb	EtOH	59	203-4	$C_{50}H_{26}Cl_4O_2S$	72.1	4.0	3.2
					(72.1	4.1	3.1)
VIIIb	AcOH	44	165-66	$C_{30}H_{26}N_2O_3$	77.4	5.3	6.3
					(77.9	5.6	6.1)
VIIIc	EtOH	57	228-29	$C_{28}H_{21}Cl_2NO$	73.2	4.6	3.2
					(73.4	4.6	3.1)
VIIId	EtOH	75	181-82	$C_{28}H_{20}Cl_2N_2O_3$	66.7	3.9	5.5
					(66.8	4.0	5.6)
IXb	EtOH	62	210-11	$C_{31}H_{19}Cl_2NO$	75.8	3.8	2.9
					(75.6	3.9	2.9)
IXc	EtOH	61	193-94	$C_{31}H_{18}Cl_2N_2O_3$	79.4	3.4	5.3
					(79.3	3.4	5.2)
Xb	EtOH	45	220-21	$C_{33}H_{23}ClN_2O_3$	74.2	4.3	5.0
					(74.7	4.3	5.3)
XIb	EtOH	35	268-69	$C_{27}H_{21}N_3O_3$	74.3	4.4	9.5
					(74.5	4.8	9.7)
XIc	EtOH	37	230-31	$C_{25}H_{16}Cl_2N_2O$	69.6	3.5	6.6
					(69.6	3.7	6.5)
XId	EtOH	39	260-61	$C_{25}H_{15}Cl_2N_3O_3$	63.1	3.3	8.7
					(63.0	3.2	8.8)
XIIb	EtOH	26	170-71	$C_{33}H_{25}N_3O_3$	77.3	4.1	8.0
					(77.5	4.9	8.2)
XIIc	EtOH	32	234-35	$C_{31}H_{20}Cl_2N_2O$	73.0	4.0	5.4
					(73.4	4.0	5.5)
XIId	EtOH	59	154-55	$C_{31}H_{14}Cl_2N_3O_3$	67.5	3.2	7.5
					(67.4	3.4	7.6)

and 2.6 (*s*, 3H, CH_3) (Found : C, 86.3; H, 5.5. $C_{27}H_{20}O_2$ requires C, 86.2; H, 5.3 %).

2-Aryl benz[f]indan-1,3-diones (III; Table 1)

Arylidene derivative (II; 0.01 mol) was heated under reflux with 2 % solution of sodium methoxide (20 ml) for 1 hr. The reaction mixture was diluted with water and acidified with dil. H_2SO_4 to give III. 6-Methyl-2-phenyl-4-(*p*-tolyl)benz[*f*]indan-1,3-dione (IIIa), obtained from IIa, was crystallized from benzene as orange crystals, yield 81 %, m.p. 145 - 46°; IR: 1690 (α, β-unsaturated C = O), 3400 (br, enolic OH)[10] (Found : C, 86.4; H, 5.3. $C_{27}H_{20}O_2$ requires C, 86.2; H, 5.3 %).

4-Aryl-3-(α-bromobenzylidene)naphtho[2,3-c]furan-1(3H)-ones (IV; Table 1)

These were prepared following the procedure reported earlier[11]. The compound IVa was crystallized from ethanol as yellow crystals, yield 85 %, m.p. 160 - 161° (Found: C, 70.9; H, 4.1. $C_{27}H_{19}BrO_2$ requires C, 71.3; H, 4.2 %).

4-Aryl-3-benzylidenenaphtho[2,3-c]furan-1(3H)-thiones (IV; Table 1)

A solution of II (0.1 mol) in xylene (50 ml) was treated with P_2S_5 (0.1 mol) and the mixture heated under reflux for 5 hr, cooled and washed with dil. Na_2CO_3. The organic layer was separated, dried (anhyd. Na_2SO_4) and concentrated. In the case of IIa, the solid product obtained was recrystallised from ethyl acetate to give Va as red crystals, yield 35%, m.p. 169 - 170°; IR: 1330 (C = S) (Found: C, 82.1; H, 4.3. $C_{27}H_{20}OS$ requires C, 82.1; H, 5.1 %).

Mercuric chloride complex (VI) of V

A solution of Va (0.01 mol) in dry ether (25 ml) was treated with excess of a saturated solution of $HgCl_2$ in dry ether at room temperature as reported earlier[12]. Removal of ether furnished a solid which was collected and washed with dry ether to give VI as dark red crystals, yield 80 %, m.p. 200 - 201° (Found: C, 48.7; H, 3.2; Cl, 10.7. $C_{27}H_{20}Cl_2OSHg$ requires C, 48.9; H, 3.0; Cl, 10.6 %).

Di-(2-aryl-1-oxobenz[f]indan-3-yl) sulphides (VII; Table 1)

A solution of V (0.001 mol) in MeOH (100 ml) was treated with NaOMe solution (0.001 mol) and the mixture heated under reflux for 30 min, cooled, diluted with water and filtered. The filtrate was acidified with dil. H_2SO_4. The solid thus separated was recrystallised from an appropriate solvent to give VII. In the case of Va, the product was crystallised from ethanol to give VIIa as dark red crystals, yield 75 %, m.p. 148 - 149°; IR : 725 (C - S - C)[13].

9-Aryl-3-benzalnaphthalimidines (VIII - X; Table 1)

A mixture of II (0.01) and fused sodium acetate (0.2 g) was fused at 180 - 200° for 2 hr and decomposed with dil. HCl to furnish a product which on recrystallization from a suitable solvent gave the title compound. VIIIa: colourless crystals from ethanol, yield 49 %, m.p. 130 - 31° (Found: C, 86.5; H, 6.5; N, 3.6. $C_{30}H_{27}NO$ requires C, 86.3; H, 6.5; N, 3.4 %); IXa: yellow crystals from acetic acid, yield 38 %, m.p. 234 - 35° (Found: C, 79.4; H, 5.4; N, 5.3. $C_{33}H_{25}N_2O_3$ requires C, 79.7; H, 5.0; N, 5.6 %); Xa: yellow crystals from ethanol, yield 62%, m.p. 257 - 58° (Found: C, 82.0; H, 4.2; N, 2.4. $C_{33}H_{24}ClNO$ requires C, 81.6; H, 4.9; N, 2.9 %); IR of VIII - X: 1740 - 1720 (α-lactam C = O).

4-Benzylnaphthalazones (XIa-d) and N-anilinonaphthalimidines (XIIa-d) (Table 1)

A solution of II (0.01 mol) in ethanol (50 ml) was treated with hydrazine hydrate or phenylhydrazine (3 ml; excess), and the mixture heated under reflux for 3 hr. The solid obtained was recrystallized from a proper solvent to give XI or XII. XIa: pale yellow crystals from ethanol, yield 52 %, m.p. 206 - 7°; IR: 1680 - 1660 (C = O of a cyclic amide)[9], 1640 - 1620 (ring C=N)[14,15]; PMR: 4.5 (*s*, 2H, Ar-CH_2-) (Found: C, 83.3; H, 5.4; N, 7.2. $C_{27}H_{22}N_2O$ requires C, 83.1; H, 5.7; N, 7.2 %). XIIa: pale yellow crystals from ethanol, yield 40 %, m.p. 253 - 54°; IR: 1740 - 1710 (cyclic imid C = O)[16]; PMR: 6.6 (*s*, 1H, olefinic proton), the singlet signal at 4.5 (Ar - CH_2-) was absent (Found: C, 84.6; H, 5.3; N, 6.0. $C_{33}H_{26}N_2O$ requires C, 85.0; H, 5.6; N, 6.0 %).

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Lead Tetraacetate Induced Ring Transformation of 6,7-Dihydro-6-arylquinazolino-[3,2-*d*][1,3,4]benzotriazepin-9(5*H*)-ones

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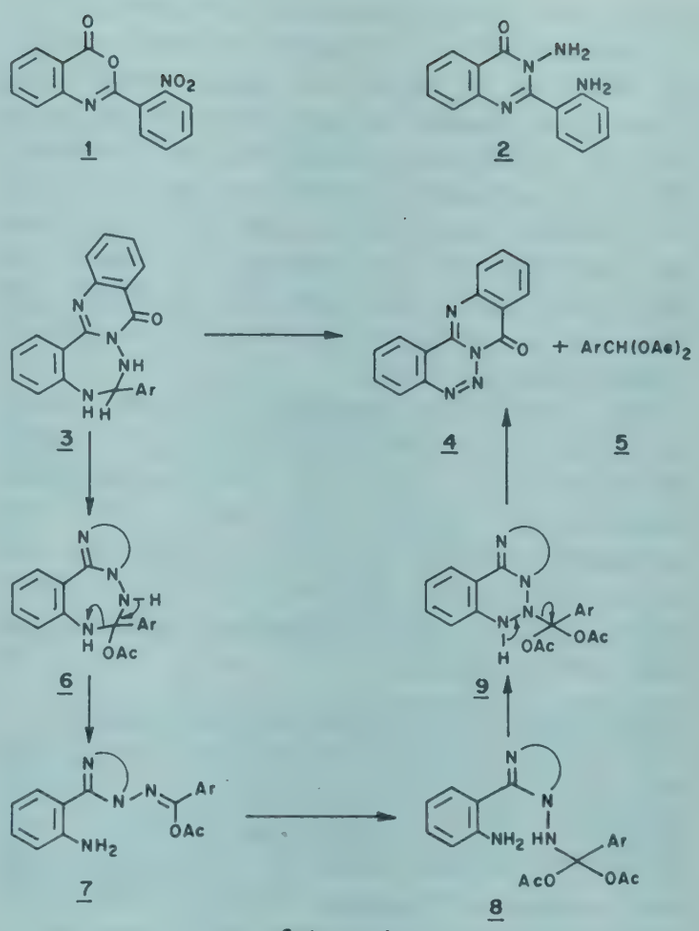
6,7-Dihydro-6-arylquinazolino[3,2-*d*][1,3,4]benzotriazepin-9(5*H*)-ones (**3a-f**) undergo ring transformation when refluxed with lead tetraacetate in benzene to give quinazolino[3,2-*c*][1,2,3]benzotriazin-8-one (**4**) along with the corresponding benzylidene diacetates (**5a-f**). Structural assignments are based on spectral data (UV, IR, PMR and mass).

1,3,4-Benzotriazepin-5-ones are known to undergo acid and base catalysed isomerisation and ring contraction reactions[1,2]. During the course of present work on the syntheses of fused 1,3,4-benzotriazepines, we observed a hitherto unknown triazepin-triazine ring transformation reaction. For example, 6,7-dihydro-6-(4′-methoxyphenyl)quinazolino[3,2-*d*][1,3,4]benzotriazepin-9(5*H*)-one (**3b**) reacted with lead tetraacetate (LTA) in benzene under reflux to yield the mono azo dye intermediate, quinazolino[3,2-*c*][1,2,3]-benzotriazin-8-one (**4**, 68%)[3-8]. 4-Methoxybenzylidene diacetate (**5b**)[9] was formed as a co-product in the reaction. Similarly, five other derivatives of **3** were reacted with LTA and in all the reactions the triazine (**4**) was isolated in 60-70% yield along with the corresponding benzylidene diacetates[9-12].

The required benzotriazepines (**3**) were prepared (Scheme 1) starting from 2-(2′-nitrophenyl)-3,1-benzoxazin-4-one (**1**)[13]. Attempts to convert the nitro group in **1** to amino group by reduction with hydrazine hydrate over Raney Ni unexpectedly resulted in the diamine (**2**) in 64% yield. This method proved advantageous than the reported procedure by Jacques Gilbert in which **2** was formed in 2% yield as one of the pyrolytic products of a anthranilic hydrazide[14]. The reaction of **2** with aromatic aldehydes in acetic acid gave **3**. The mass spectrum of **3b** showed a prominent ion at *m/z* 237 [2-(2′-aminophenyl)quinazolin-4(3*H*)-one structure] formed by loss of 4-$H_3COC_6H_4CN$ from $M^{+\cdot}$. However, dry pyrolysis of **3b** at 220°C yielded an intractable tarry material.

The mechanism of the formation of 4 from 3 could be rationalised through the intermediates **6-9** as shown in Scheme 1. Lead tetraacetate acetoxylates the active methine carbon in **3** in the initial step to give **6** which isomerises to the more stable **7**. The hydrazone (**7**) may add on acetic acid to give the diamine derivative (**8**). LTA is known to mediate dimerisation of aniline through PhNH radicals[15]. By analogy, **8** may cyclise to **9** which gives the product **4** by 1,2-elimination of benzylidene diacetate.



Scheme 1

6,7-*Dihydro*-6-*arylquinazolino*[3,2-*d*][1,3,4]*benzotriazepin*-9(5*H*)-*ones* (**3**): (*a*) 3-*Amino*-2-(2′-*aminophenyl*)-*quinazolin*-4(3*H*)-*one* (**2**)

To a solution of 2-(2′-nitrophenyl)-3,1-benzoxazin-4-one (1 g, 3.73 mmol) in hot dioxane (10 ml), Raney Ni (0.5 g)[16] and hydrazine hydrate (99-100%, 0.5 ml) were added and the reaction mixture was allowed to stand at room temperature for 30 min and thereafter refluxed on a steam-bath for 3 hr. The reaction mixture was filtered, the filtrate concentrated and poured into ice cold water (100 ml). A brown solid (1 g) separated which was filtered and refluxed in excess hydrazine hydrate (99-100%, 10 ml) for 2.5 hr. On cooling the reac-

tion mixture, **2** separated out, which was filtered, dried and recrystallised from methanol, m.p. 228° (lit.[14] 228-29°).

(b) Reaction of **2** *with aldehydes. Formation of* **3**

A mixture of **2** (1 g, 4 mmol) and the appropriate aldehyde (4 mmol) in glacial acetic acid (10 ml) was warmed at steam-bath temperature for 2 hr, cooled and poured into ice cold water (50 ml). Compound (**3**) which separated out from was filtered, washed with water (100 ml), dried and recrystallised from appropriate solvent. **3b** was characterised based on UV, IR, PMR and mass, and the structures of **3a** and **3c-f** were assigned by analogy (Table 1).

3b: MS: *m/z* (rel. intensity) 370 ($M^{+\cdot}$, 38%), 369 (24%), 237 (100%), 236 (74%), 119 (84%); PMR($CDCl_3$): δ 1.6 (*s*, 1H, NH, exchangeable with D_2O), 3.7 (*s*, 3H, OCH_3), 4.03 (*s*, 1H, NH, exchangeable with D_2O), 5.4 (*s*, 1H, benzylic), 7.0-8.5 (*m*, 12H, Arom); IR(KBr): 3310, 3210, (*ν*NH), 1650 cm^{-1} (*ν*C=O); UV(solvent): 292 (log ε 4.45), 348 nm (3.72).

Quinazolino[3,2-c][1,2,3]benzotriazin-8-one (**4**)

A mixture of **3** (0.5 g) and lead tetraacetate (1.5 g) was heated in dry benzene (25 ml) under reflux for 2 hr. The solvent was removed *in vacuo* and the residual solid was chromatographed over a column of silica gel (200 mesh) using benzene (10×20 ml) as eluent. Quinazolino-[3,2-*c*][1,2,3]benzotriazin-8-one (**4**) (3-10 fractions) and corresponding benzylidene diacetate (**5**) (1 and 2 fractions) were isolated and recrystallised from benzene and pet. ether (60-80°) respectively.

4: m.p. 216° (lit.[4] m.p. 214-16°); MS: *m/z* (rel. inten %) 248 ($M^{+\cdot}$, 22), 220 (100), 192 (46), 76 (36), 28 (72); IR(KBr): (νC=N), 1650 (νN=N), 1700 cm^{-1} (νC=O); PMR($CDCl_3$): δ 7.1-8.2 (*m*, aromatic). Melting points of benzylidene diacetates (**5a-f**): **5a**, 45° (46°)[9]; **5b** 65 (67°)[9]; **5c** 69° (69°)[10]; **5d** 81° (82°)[11]; **5e** 124° (126.5°)[12]; and **5f** 89° (90°C)[12].

Table 1—6,7-Dihydro-6-arylquinazolino[3,2-*d*][1,3,4]-benzotriazepin-9(5*H*)-ones

Compd **3**	Ar	m.p. (°C)	Yield (%)	N found (Calc), %
a	C_6H_5	140[i]	80	16.78 (16.47)
b	4-$H_3COC_6H_4$	170[i]	83	15.58 (15.13)
c	4-$H_3CC_6H_4$	180[ii]	85	15.82 (15.81)
d	4-ClC_6H_4	183[ii]	81	15.25 (14.97)
e	4-$O_2NC_6H_4$	223[ii]	84	18.31 (18.18)
f	2-$O_2NC_6H_4$	244[ii]	83	18.36 (18.18)

Recrystallised from: **a**, **b** benzene; and **c-f** pet. ether-chloroform (3:1), melting points are uncorrected.

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Reaction of Dichlorocarbene with 2-Chloro-N-methylbenzimidazole — A Different Course

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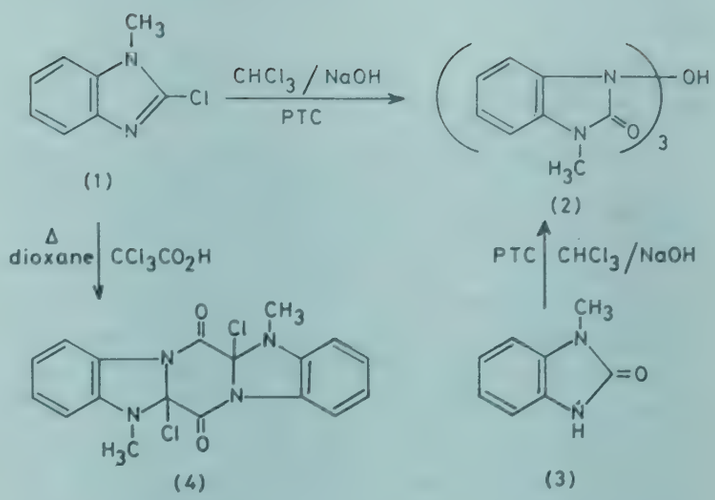
Reaction of dichlorocarbene with 2-chloro-N-methylbenzimidazole under PTC in aqueous medium affords tris(N-Methylbenzimidazole-2-one-1-yl) methane (**2**). The same reaction in a non-aqueous medium furnishes 5a,12a-dichloro-5,12-dimethyl-5a,12a-dihydropyrazino[1,2*a*: 4,5*a*] bis-benzimidazole-6(*H*), 13(*H*)-dione (**4**).



Carbenes have emerged as useful species for a variety of synthetic transformations in organic chemistry[1]. Carbenes undergo insertion reactions between many bond types[2], react with nucleophiles to give ylids[3] and have the ability to insert between C − H bonds and bring about ring expansion via addition to C = C bonds[4,5] in heterocyclic compounds. Dichlorocarbene, the most versatile amongst carbenes, has been intensively studied and extensively used in organic synthesis. However, there have been only few reports of its reaction with C = N bond in heterocyclic compounds[6]. In the course of our investigations on the reaction of dichlorocarbene with benzazoles[7] and in consideration of the results obtained, we describe herein an unusual reaction of dichlorocarbene with 2-chloro-N-methylbenzimidazole (**1**).

The reaction of **1** with dichlorocarbene (generated *in situ* from chloroform and aqueous sodium hydroxide) in the presence of triethylbenzylammonium chloride (TEBA) and triethylenediamine under phase transfer catalysis afforded a product, after usual work-up, in 41% yield. The product was characterised as tris(N-methylbenzimidazole-2-one-1-yl) methane (**2**) on spectral evidences. Further support was provided by isolating **2** in good yields from the reaction of N-methylbenzimidazol-2-one (**3**) with dichlorocarbene under identical reaction conditions.

When the reaction of **1** with dichlorocarbene was carried out with sodium trichloroacetate in dry dioxane at 100°C, no trace of **2** was observed, instead a novel pentacyclic compound 5a,12a-dichloro-5,12-dimethyl-5a,12a-dihydropyrazino[1,2-*a*: 4,5-*a*']bisbenzimidazole-6(*H*),13(*H*)-dione (**4**) was isolated in 10% yield. The structure of **4** was arrived at from its elemental analyses and spectral data. The high resolution mass spectral data showed the molecular ion at *m/z* 388.0517 (M^+) (calc. *m/z* 388.0492) which is in agreement with the molecular formula $C_{18}H_{14}Cl_2N_4O_2$. The peak intensities at *m/z* 390 (M + 2) and 392 (M + 4) which were in the ratio of 70:10 revealed the presence of two chlorine atoms. Further confirmation was derived from the fragmentation pattern.

This result clearly indicates that alkali-free reaction medium cannot produce the tris-compound **2** from **1** and dichlorocarbene, since the initial hydrolysis step is prevented. It is interesting to note that in the absence of alkali, the reaction of **1** with dichlorocarbene takes a different course, probably through initial addition of carbenoid to the azomethine nitrogen. Finally, the structure of **4** was confirmed by comparing with the parent pentacyclic compound reported by Copeland[8], in the reaction of benzimidazole-2-carboxylic acid with thionyl chloride.

Dichlorocarbene reaction with 2-chloro-N-methylbenzimidazole (**1**): (*a*) *In aqueous alkaline medium*

To 2-chloro-N-methylbenzimidazole (1 g) in chloroform (20 ml) were added the phase transfer catalyst, TEBA (0.013 g) and triethylenediamine (0.006 g). Sodium hydroxide (35%, 1.2 ml) was added dropwise to the above solution and stirred at room temperature for 8 hr. The two layers were separated and the chloroform was distilled off from the organic layer. The crude product (**2**) obtained was purified on a silica gel column with benzene and ethyl acetate (3:1) as the eluent; yield 0.32 g (41%); m.p. 192°C; IR (KBr) 1700, 1660, 1480 and 1100 cm^{-1}; PMR ($CDCl_3$): δ 3.8 (*s*, 9H, N − CH_3), 6.9-7.9 (*m*, 12H, aromatic H), 8.84 (*s*, 1H, CH); ^{13}C NMR ($CDCl_3$): δ

26.71 ($N-CH_3$), 107.17 (CH), 108.25, 108.57, 120.10, 120.44, 127.81 and 130.57 (benzimidazolyl carbons), 154.09 ($C=O$); (*m/z*, rel. int. %): 454 (M^+, 10(for $C_{25}H_{22}N_6O_3$, 308 (25), 307 (100), 205 (5) and 160 (2).

(*b*) *In anhydrous medium*

To 2-chloro-N-methylbenzimidazole (1 g) in dry dioxane (20 ml) was added sodium trichloroacetate (2.21 g) and refluxed at 100°C with stirring for 14 hr. The sodium salt formed was filtered and the dioxane distilled. The crude material (**4**) was purified on a silica gel column with ethyl acetate as the eluent; yield 0.116 g (10%); IR ($CHCl_3$): 1700, 1400, 1320 and 1110 cm^{-1}; PMR ($CDCl_3$): δ 3.2 (*s*, 6H, $N-CH_3$), 6.7-7.3 (*m*, 8H, aromatic H); MS (*m/z*, rel. int. %): 388 (M^+, 9.6; calc for $C_{18}H_{14}Cl_2N_4O_2$), 390 (M + 2) (70% of M^+), 392 (M + 4) (10% of M^+), 353 (1.43), 318 (0.4) and 166 (16.05).

The award of research fellowship to JSR by the CSIR, New Delhi is gratefully acknowledged.

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Improved Procedure for Attachment of Amino Acids to Polymer in Peptide Synthesis by Liquid-Phase Method

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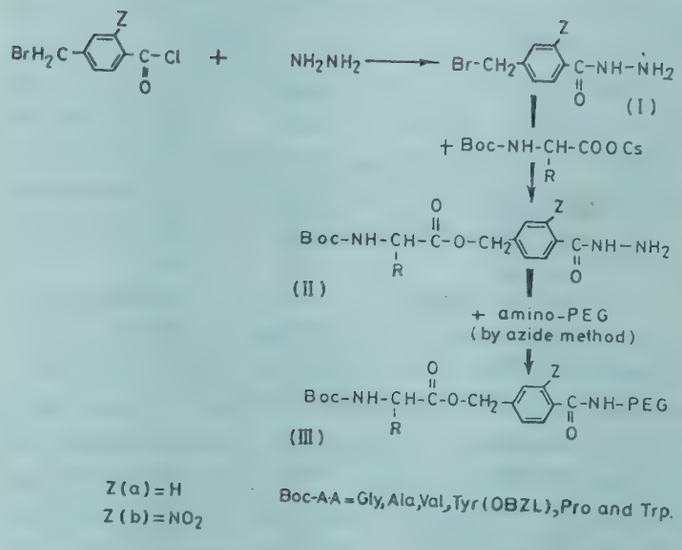
An improved procedure for attachment of protected amino acids to polyethyleneglycol through benzyl and nitrobenzyl ester links is described. The amino acids to be attached to the polymer [Boc-Gly, Boc-Ala, Boc-Val, Boc-Tyr (OBZL), Boc-Pro and Boc-Trp] are first converted into their cesium salts and then esterified with *p*-bromomethylbenzoyl hydrazide. The esterification reaction is simple and proceeds under mild condition without observable racemization. The esters obtained are coupled to aminopolyethyleneglycol by the azide method. This procedure allows complete reaction of bromomethyl group with the protected amino acid before attachment to the polymer, thereby avoiding side reactions.

In liquid-phase method[1] (LPM) of peptide synthesis, benzyl group is attached to aminopolyethyleneglycol (amino-PEG) resulting in a chemically more stable amide bond between polyethyleneglycol (PEG) and the anchoring group. The attachment of COOH-terminal of the protected amino acid to the polymer is achieved by reacting its cesium salt in excess (5 mmol Boc-amino acid cesium salt for 1 mmol polymer) with the terminal bromomethyl group.

A photosensitive anchoring group (like 3-nitro-4-bromomethylbenzoyl) is attached to the PEG[2] for facilitating the removal of the protected peptide from the resin by photolysis at 3500 Å under mild condition.

However, one of the problems that is encountered is the incomplete esterification of the polymer with the anchoring group in the first step and the low yield of incorporation of the first Boc-amino acid into the polymer in the second step leading to failure sequences during synthesis[3a,4]. In such cases quantitative yield can be achieved only by employing large excess of reagent and prolonged reaction times. However, this may lead to side reactions or racemization.

To overcome some of these problems we have developed a procedure for esterification of Boc-amino acids (Boc-Gly, Boc-Ala, Boc-Val, Boc-Tyr (OBZL), Boc-Pro and Boc-Trp) with the two main anchoring groups used in LPM of peptide synthesis (benzyl and nitrobenzyl ester links).



Scheme 1

The general procedure is as follows: the carboxylic acid to be esterified is first converted into its cesium salt by titration[4] to neutrality with aqueous Cs_2CO_3. After evaporation and dryness, the neutral salt is treated with *p*-bromomethylbenzoyl hydrazide or with 3-nitro-4-bromomethylbenzoyl hydrazide in DMF at 40° to obtain the corresponding ester as shown in Scheme 1. The resulting hydrazides are coupled to the amino PEG in DMF using the azide method[5].

The above reactions are simple and proceed without observable racemization[6] (racemization was below the limits of detection by Manning and Moore test[6]). Many amino acids that might be difficult to incorporate into the *p*-bromomethylbenzoyl polyethyleneglycol have now been incorporated in good yield without employing large excess of the reagent or high temperature.

Melting points are uncorrected. TLC was carried out on precoated silica gel plates (Merck, 60) with butanol-acetic acid-water (30 : 10 : 10, v/v) as the solvent system. Elemental analyses were performed in Microanalytical Laboratory, Mansoura University. Amino acid analyses were carried out on a Beckmann-Unichrom analyzer.

All the new compounds were routinely examined by IR (Perkin-Elmer infracord) and UV (Beckmann model 25) spectroscopy and the spectra were compatible with the assigned structures. The Boc-amino acids were prepared according to Shnabel[7].

p-Bromomethylbenzoyl hydrazide

p-Bromomethylbenzoyl chloride[8] (2.3 g, 0.01 mol) was added in portions, with stirring, to hydra-

Table 1—Reaction of Boc-amino Acids with *p*-Bromomethylbenzoyl hydrazide (Ia) and 3-Nitro-4-bromomethylbenzoyl hydrazide (Ib) and Formation of Boc-A.A Esters (IIa and IIb series)

Boc-A.A	Ester (II)*	
	Yield %	m.p. (°C)
Reaction with Ia (Z = H)		
Boc-Gly	92	Oil
Boc-Ala	94	Oil
Boc-Val	96	Oil
Boc-Tyr (OBZL)	88	97-99
Boc-Pro	82	Oil
Boc-Trp	79.1	108-10
Reaction with Ib ($Z = NO_2$)		
Boc-Gly	91	Oil
Boc-Ala	87	Oil
Boc-Val	93	Oil
Boc-Tyr (OBZL)	89	122-24
Boc-Pro	84	Oil
Boc-Trp	82	115-17

*Satisfactory elemental analyses have been obtained for these compounds.

Table 2—Reaction of Produced esters (II) with Amino Polyethyleneglycol (amino-PEG, III)

Boc-A.A	Incorporation* of ester with amino PEG (%)
From IIa Series	
Boc-Gly	100
Boc-Ala	98
Boc-Val	98
Boc-Tyr (OBZL)	87
Boc-Pro	85
Boc-Trp	70†
From IIb Series	
Boc-Gly	100
Boc-Ala	97
Boc-Val	97
Boc-Tyr (OBZL)	92
Boc-Pro	88
Boc-Trp	85

*Percentage incorporation is determined by amino acid analyses.
†Alkaline hydrolysis causes at least 15% loss of Trp[3b].

zine hydrate (0.05 mol) in absolute ehtanol (3 ml) at 0°. The reaction mixture was dried by suction, the residue dissolved in dry DMF and filtered. Evaporation of the solvent under reduced pressure afforded the desired compound as a yellow crystalline powder; yield 88.29% (2.6 g); m.p. 218-20° (Found: C, 42.0; H, 3.6; N, 12.4. Reqd: C, 41.9; H, 3.4; N, 12.2%).

3-Nitro-4-bromomethylbenzoyl hydrazide

3-Nitro-4-bromomethylbenzoyl chloride[3] (2.79 g, 0.01 mol) was added in portions with stirring to hydrazine hydrate (0.05 mol) in absolute ethanol (3 ml) at 0°, work-up as described above afforded the desired compound in a yellow amorphous powder, yield 89.77% (2.5 g) (Found: C, 36.0; H, 2.7; N, 15.0. Reqd: C, 35.0; H, 2.9; N, 15.3%).

Esterification of Boc-amino acids with p-bromomethylbenzoyl hydrazide or 3-nitro-4-bromomethylbenzoyl hydrazide: General procedure

A solution of cesium salt (5 mmol) of protected amino acid in dry DMF was added to a solution of *p*-bromomethylbenzoyl hydrazide (1 mmol) in dry DMF (10 ml) and refluxed for 48 hr at 40°. The solvent was evaporated under reduced pressure and the residue was centrifuged with water to obtain the ester (see Table 1).

Coupling of Boc-amino acid benzoyl hydrazide to amino-PEG by the azide method

A precooled (−5°C) solution of Boc-amino acid benzoyl hydrazide (0.54 mol) in DMF (10 ml) was treated with 2.36 *N* HCl (0.46 ml) in THF followed by 0.073 ml of isoamyl nitrile. After 10 min the mixture was cooled down to −30° and to this were added amino PEG (0.36 mmol, mol wt, 5000) and triethylamine (1.08 mmol) in DMF (10 ml). The mixture was stirred gently at 4° for 36 hr during which time some more Et_3N was added in order to maintain the *p*H slightly basic. The solvent was evaporated, the residue dissolved in CH_2Cl_2 and precipitated by adding dry ether and filtered. The last step was repeated twice till pure product was obtained (see Table 2).

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Circular Dichroic & Carbon-13 Studies of Antiarrhythmic Peptide††

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Solvent dependent conformational distribution of antiarrhythmic peptide has been studied using CD and ^{13}C NMR spectroscopy. The CD spectra in H_2O, MeOH and TFE show predominance of polyproline II-like structure. Solvent titration experiments in methanol-water system using ^{13}C NMR suggest that all the carbonyls are exposed and are not involved in any ordered structure. Further, the $\Delta\delta_{\beta\gamma}$ value for Pro^2 corresponds to the dihedral angle, close to the value of 150° for polyproline II-like structure, thereby suggesting that in solution AAP exists predominantly in polyproline II-like structure.

Aonuma and coworkers[1] recently isolated a peptide from bovine atria. The peptide which exhibited both antiarrhythmic and antithrombotic activities[2,3], was designated as antiarrhythmic peptide (AAP) and characterised as a hexapeptide having the amino acid sequence Gly-Pro-Hyp-Gly-Ala-Gly[4]. Since AAP contains two imino acids Pro and Hyp at positions 2 and 3 respectively, and has no reactive functionality on the side chains of other amino acids, it is possible that the manifestation of its specific biological activity may be a function of some well-defined secondary structure(s) in solution. To investigate this point we decided to undertake studies on the conformation of AAP in solution using ^{13}C NMR and CD spectroscopy. Recently CD has been effectively used to detect intramolecularly H-bonded conformations in equilibrium in solution even in the case of small peptide[5-9].

AAP was synthesised and characterised by the literature procedure[10]. CD spectra were recorded on a Jobin Yvon Mark III dichrograph using solutions containing 1 mg AAP/ml. The band intensities are expressed as molar ellipticities $[\theta]_M$ in deg cm^2 dmol^{-1}. Carbon-13 NMR spectra (100 MHz) were recorded on Bruker WM 400 FT NMR spectrometer; chemical shifts are expressed as δ(ppm), downfield from CH_3OH when CH_3OH was used and as the solvent and *p*-dioxane when H_2O was used on the solvent. Most of the resonance assignments are based on the data obtained from intermediate fragments or from data available in literature on Pro-Hyp[11]. *p*H titration studies were accomplished with minimum sample dilution of stock solution of 6N NaOH and 6N HCl. *p*H values were not changed monotonically but were varied somewhat randomly between the extreme values of 1.0 and 11.0.

CD Spectra

The CD spectrum of AAP in MeOH (Fig. 1, curve a) exhibits a maximum at 220 nm and a small minimum near 235 nm while a strong −ve trend may be anticipated around 200 nm. The band near 235 nm may be due to a γ-turn (C_7) fixed by an intramolecular H-bond (3 → 1) between CO of Pro^2 and the NH of Gly^4. This assumption is based on previous reports on bradykinin[12], proline derivatives[13] and Pro containing tetra peptides[9] where this band has been attributed to a γ-turn. On the other hand, a strong +ve band at 220 nm and a large −ve band around 200 nm is characteristic of native collagen[14] and polyproline II-like structure[7,9]. Thus, in methanol the CD pattern may be explained on the basis of a conformational equilibrium existing between a polyproline II-like extended structure and possibly a (C_7) γ-turn. Drieding model of AAP indicates intramolecular H-bonding between CO of Pro^2 and NH of Gly^4.

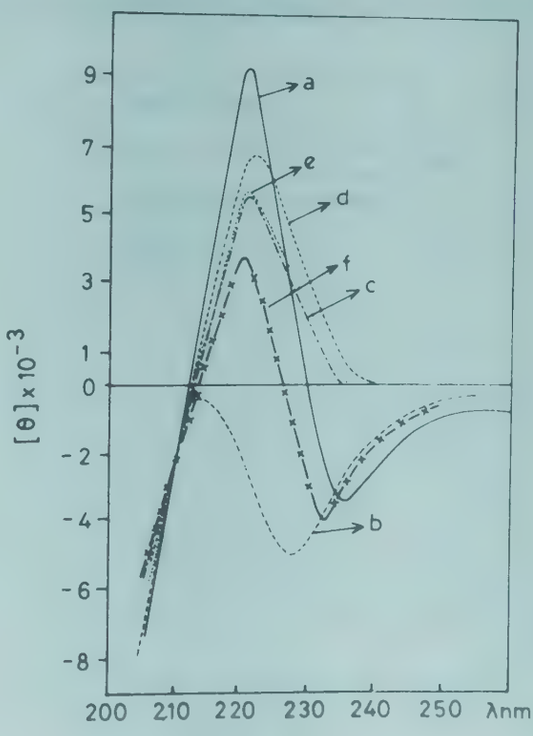

Fig. 1 — CD spectra of AAP in MeOH (curve a), TFE (curve b), *p*H 7.0 (curve c), *p*H 4.0 (curve d), *p*H 11.0 (curve e) and MeOH-TFE (1:1) (curve f).

†CDRI communication No. 3846

‡Abbreviations for amino acid are according to IUPAC-IUB Commission on biochemical nomenclature Biochemistry, 11 (1972) 1726. Other abbreviations are MeOH (methanol) and TFE, trifluoroethanol.

However, CD spectra in water at *p*Hs 7, 4 and 11 (Fig. 1, curves c-e) show that the conformational distribution shifts to populate polyproline II-like structure, which is evident from the disappearance of the 235 nm band and the presence of a + ve band at 220 nm and a − ve band at 200 nm. On the contrary, in TFE (curve b) the + ve band at 220 nm completely disappears leaving − ve trough at 227 nm which undergoes blue shift by 8 nm and a strong − ve trend around 200 nm. This suggests that the peptide undergoes a large conformational change on going from MeOH to TFE. Interestingly, the spectrum in 1:1 MeOH-TFE exhibits CD bands (Fig. 1, curve f) characteristic of both solvents, suggesting that different conformational states may be populated.

Since it is well established that CD alone cannot provide definite information about the conformational features of small peptides, we have also carried out ^{13}C NMR studies with a view to get additional information regarding the solution conformation of AAP.

Carbon-13 NMR studies

pH titration

The 100 MHz ^{13}C NMR spectrum of AAP displayed six carbonyl carbon resonances between 174.33 and 163.95. A complete *p*H titration of the carbonyl resonances was undertaken in order to assign various carbonyls. The *p*H-dependence of carbonyl peak is shown in Fig. 2. The carbonyl peaks of Gly 1, Pro 2, Ala 5 and Gly 4 residues are readily distinguishable by their *p*H behaviour. Remaining carbonyl peaks were assigned on the basis of a comparison of the shifts with the data obtained from fragments Gly-Pro-Hyp, Gly-Pro-Hyp-Gly, Hyp-Gly-Ala-Gly, Pro-Hyp-Gly-Ala-Gly (unpublished data). Such experiments have been carried out earlier by London *et al.*[15] for assigning carbonyls of bradykinin.

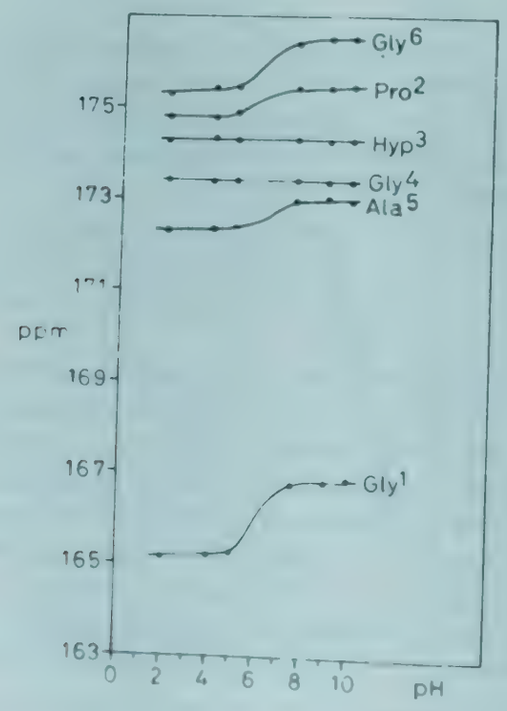

Fig. 2 — *p*H dependence of carbonyl peaks

Solvent dependence of carbonyl peaks

The observed ^{13}C shift for carbonyl resonances of AAP in methanol and water are given in Table 1.

Table 1 — Carbon-13 Chemical Shifts of Carbonyl Carbons of AAP

Carbonyl	Water	Methanol	Δδ
Gly^1	165.25	163.95	1.3
Ala^5	172.31	171.11	1.2
Gly^4	173.42	171.92	1.4
Hyp^3	174.34	173.04	1.3
Pro^2	174.90	173.75	1.2
Gly^6	175.43	174.23	1.2

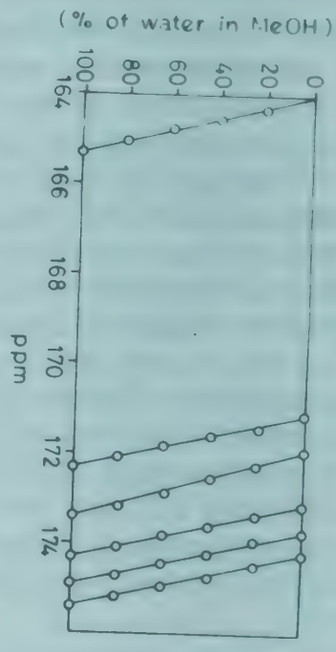

Fig. 3 — Solvent titration of carbonyl region of AAP in MeOH/water

Solvent titration experiments carried out in water-methanol mixtures of varying compositions, confirmed the absence of any crossover of peaks on going from water to methanol (Fig. 3). All the carbonyl resonances experience similar upfield shifts as the solvent composition changes from water to methanol. Similar upfield shifts have been observed by other workers for the carbonyl resonances in a variety of peptides[16,17]. These results suggest that in solution AAP assumes a conformation in which all the carbonyls are exposed almost to the same extent and form hydrogen bonds primarily with solvent. Fur-

ther, we have also calculated the dihedral angle ψ about the Pro C^{α}-Co bond in order to establish the predominant conformer of AAP in solution using chemical shift data obtained for Pro[18]. We measured $\Delta\delta_{\beta\gamma}$ for Pro[2] of AAp in MeOH and H_2O. The observed values were 3.86 and 3.97 corresponding to the ψ value of 147° and 150° respectively. These values correspond to the dihedral angle ψ in polyproline II-like structure ($\psi = 150°$, Hollosoi *et al.*[9]) around Pro C^{α}-CO bond. Thus ^{13}C NMR studies indicate that in solution AAP exists predominantly in a polyproline II-like conformation.

Our CD data, thus, indicate that the secondary structure of AAP in organic solvents is a time average of two interconverting structures — one polyproline II-type and the other partially ordered due to a hydrogen bonded (C_7) configuration. In water, however, equilibrium shifts to populate the polyproline II-like structure. On the other hand, ^{13}C NMR shifts of Pro C^{β} and C^{γ} resonances and solvent dependent shifts of all the carbonyl resonances indicate that AAP exists exclusively in a polyproline II-like structure both in MeOH as well as in H_2O. Thus, our CD and ^{13}C NMR studies suggest that AAP exists predominantly in a polyproline II-like structure in solution. Any ordered structure that exists will only be significant for such a fraction of time that it can hardly be reflected unequivocally in the NMR parameters.

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Reaction of Cerium(IV) Ammonium Nitrate with Aralkyl & Aromatic Ketones

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Fluoren-9-one on treatment with cerium(IV) ammonium nitrate (CAN) yields five compounds which have been identified as 3-nitro-; 2-nitro-; 1,8-dinitro-; 2,7-dinitro; and 2,5-dinitrofluoren-9-ones. Acetophenone on treatment with CAN, yields only benzoic acid while 2,4-dihydroxyacetophenone on similar treatment yields three compounds which have been identified as 2,4-dihydroxy-5-nitro-; 2,4-dihydroxy-3-nitro-; and 2,4-dihydroxy-3,5-dinitro-acetophenones.

In this note we report our results on the reactions of cerium(IV) ammonium nitrate with fluoren-9-one, acetophenone and 2,4-dihydroxyacetophenone. The resulting nitro substituted derivatives which are otherwise extremely difficult to obtain, have been characterised by elemental analyses, spectral data and comparison with authentic samples.

To a solution of the substrate in acetic acid (2 g, 5-10 ml) was added a strong, hot solution of cerium(IV) ammonium nitrate in acetic acid (5 g, 30-40 ml). The solution was warmed on a water-bath while the mixture was stirred continuously (30 min-2 hr) with TLC monitoring using benzene-ethyl acetate (2:8) as the developing solvent. The reaction mixture was cooled, poured onto crushed ice (50-60 g) and extracted with ethyl acetate. The organic extract was concentrated under reduced pressure to yield a solid which was subjected to column chromatography (silica gel) using petroleum ether, benzene and ethyl acetate either pure or as mixtures of suitable ratios in increasing order of polarity for elution. Eluates collected from each fraction (100 ml) were concentrated under reduced pressure and the fractions giving single spots were recrystallized from solvents mentioned under each compound in yields given along with their description.

Reaction products of fluoren-9-one

Fluoren-9-one yielded a mixture of five compounds A_1-A_5.

Compound A_1 (0.5 g), m.p. 230°, was obtained as yellowish brown needles from pet. ether-benzene (95:5) and gave positive test for carbonyl function (2,4-DNP) and positive Lassaigne's test for nitrogen and an M^+ ion at *m/z* 226 (100%) in its mass spectrum. It was finally characterized as 3-nitrofluoren-9-one (lit.[1,2] m.p. 232°); oxime, m.p. 216-17° (yellow brown needles from ethanol) (lit.[1,2] m.p. 217°).

Compound A_2 (0.56 g), m.p. 196°, was crystallised from pet. ether-benzene (8:2). It gave positive Lassaigne's test for nitrogen and 2,4-DNP test for the carbonyl functionality and an M^+ ion at *m/z* 270 (100%) in its mass spectrum. It was identified as 1,8-dinitrofluoren-9-one (lit.[1,2] m.p. 197°) and identity was further confirmed by the preparation of its oxime which crystallised from ethanol, m.p. 246° (lit.[2] m .p. 250°C).

Compound A_3 (0.52 g), m.p. 215-18°, was obtained from benzene-pet. ether (1:1) eluate and gave positive 2,4-DNP test for carbonyl function. It analysed for $C_{13}H_7NO_3$ and was identified as 2-nitrofluoren-9-one (lit.[1,2] m.p. 222°) by analysis of PMR and IR spectra and the identity confirmed by the preparation of its oxime, m.p. 256° (lit.[1,2] m.p. 258°).

Compound A_4 (0.07 g), m.p. 241°, was crystallised from pet. ether-benzene (2:7) as pale yellow prisms and gave positive 2,4-DNP test for the carbonyl function. It analysed for $C_{13}H_6N_2O_5$ and its structure was established as 2,5-dinitrofluoren-9-one (lit.[1,2] m.p. 243°) which was confirmed by preparation of its oxime, m.p. 264° (lit.[1,2] m.p. 265°).

Compound A_5 (0.100 g) m.p. 296-97°, was obtained as yellow needles from benzene. It gave positive 2,4-DNP test for carbonyl function and analysed for $C_{13}H_6N_2O_5$. Its identity as 2,7-dinitrofluoren-9-one (lit.[1,2] m.p. 290°) was established by preparation of its phenylhydrazone which crystallised from ethanol, m.p. 261° (lit.[1,2] m.p. 263°).

Reaction product of acetophenone

Acetophenone when treated with CAN gave only one compound which was crystallised as white needles from pet. ether-benzene (8:2), m.p. 120-21°. It gave effervescence with $NaHCO_3$ solution and analyzed for $C_7H_6O_2$. It was identified as benzoic acid by comparison with an authentic sample (m.p., m.m.p.).

Reaction products of 2,4-dihydroxyacetophenone

2,4-Dihydroxyacetophenone when treated with

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CAN gave a red brown mixture from which three compounds A_7-A_9 could be obtained which were identified as follows:

Compound A_7 (0.8 g), m.p. 143°, was obtained as yellow prisms from pet. ether which gave positive ferric chloride test for phenols and Lassaigne's test for nitrogen. It analysed for $C_8H_7NO_5$. Its structure as 2,4-dihydroxy-5-nitroacetophenone (lit.[3] m.p. 142°) was established by direct comparison with an authentic sample (co-IR, PMR, m.p., m.m.p., co-TLC).

Compound A_8 (0.6 g), m.p. 90-91°, was obtained as yellow needles from pet. ether-benzene (95.5) and gave positive test for phenolics. It analysed for $C_8H_7NO_5$. Its structure as 2,4-dihydroxy-3-nitroacetophenone (lit.[3] m.p. 93°) was established by direct comparison with authentic synthetic sample (m.m.p., m.p., PMR and co-IR).

Compound A_9 (0.7 g), m.p. 168°, was obtained from pet. ether-benzene (8:2) as yellow prisms and gave positive ferric chloride test for phenolics. It analysed for $C_8H_6N_2O_7$. Its identity as 2,4-dihydroxy-3,5-dinitroacetophenone (lit.[3] m.p. 167°) was confirmed by comparison with an authentic sample (co-IR, PMR, m.m.p., co-TLC).

This constitutes the first one pot cerium(IV) induced synthesis of the listed compounds.

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Reactions of Aromatic N-Oxides with 2-Thiobarbituric Acid in the Presence of Acetic Anhydride

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Quinoline N-oxides (**1**) react with 2-thiobarbituric acid (**2**) in Ac_2O-DMF or in Ac_2O alone to afford regioselectively 2-substituted quinolines (**3**) or quinolinium ylides (**4**) depending on the nature of **1** and the reaction conditions. The reaction of quinoline, lepidine, 4-chloroquinoline and 4-methoxyquinoline N-oxides with **2** in Ac_2O-DMF at room temperature or at 90° gives the corresponding N-ylides (**4**). The directive influence of the reaction medium becomes reverse when Ac_2O is used alone at room temperature or at 90°. While 3-cyanoquinoline N-oxide (**1g**) gives only 2-substituted quinoline (**3g**), 4-morphilino- and 3-bromo-quinoline N-oxides (**1e, f**) afford N-ylides (**4e, f**) independently of the reaction conditions. Furthermore, isoquinoline 2-oxide (**7**) readily reacts with **2** under different conditions to give invariably the 1-substituted isoquinoline (**8**). Pyridine N-oxide gives only 5-dimethylaminomethylene-2-thiobarbituric acid (**9**) on reaction with **2** in Ac_2O-DMF at room temperature.

As an extension of our studies on the reaction of aromatic N-oxides with heterocyclic compounds containing an active methylene group in the presence of acetic anhydride[1-4], we have now carried out reactions using 2-thiobarbituric acid (**2**) as an active methylene compound. The results are reported in this note.

Quinoline N-oxide (**1a**) when treated with **2** at 90° in the presence of acetic anhydride alone afforded 5-(2-quinolyl)-2-thiobarbituric acid (**3a**). On the other hand, heating of **1a** with **2** in acetic anhydride (1.2 eq.)-DMF at 90° for 3 hr, gave quinolinium N-[5-(2-thio)barbituric acid]ylide (**4a**). Same results were obtained when the reaction was carried out at room temperature.

Compounds **3a** and **4a** were characterized by elemental analyses, spectral data and chemical reactions. While the signal due to C_2-H proton of quinoline ring was not noticed in the PMR spectrum of **3a**, it appeared at δ 9.21-9.32 as a multiplet in the case of **4a**. The UV spectrum of **3a** was quite different from that of **4a**, but it was similar to that of 2-(2-quinolyl)cyclohexane-1,3-dione[5]. Compound **3a** on oxidation with 30% hydrogen peroxide gave 5-(1-oxido-2-quinolyl)-2-thiobarbituric acid (**5**) contrary to 2-substituted quinoline analogues which invariably produced[3] quinaldic acid N-oxide. The oxidation of **4a** under similar conditions yielded **1a** along with the N-ylide reported earlier[6]. It was further ascertained that **3a** was not identical with 5-(4-quinolyl)-2-thiobarbituric acid (**6**), prepared by heating 4-chloroquinoline with the sodium salt of **2** in DMF.

In order to explore the effect of substituents on the reaction course, the reactions of some 4- and 3-substituted quinoline N-oxides (**1a-g**) with **2** were carried out principally in Ac_2O (1.2 eq.)-DMF at room temperature or at 90° and also in acetic anhydride alone at 90°. The results are given in Table 1.

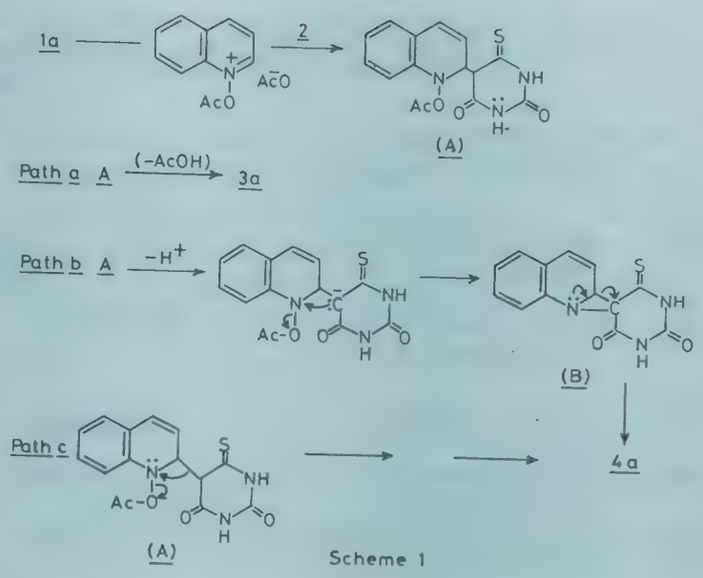
Lepidine, 4-chloro- and 4-methoxyquinoline N-oxides (**1b-d**) afforded 2-substituted quinolines (**3b-d**) and N-ylides (**4b-d**), respectively when the reaction was carried out in acetic anhydride alone and in Ac_2O (1.2 eq.)-DMF. However, 4-morpholino- and 3-bromo-quinoline N-oxides (**1e, f**) gave only the corresponding N-ylides (**4e** and **4f**) inde-

pendently of the reaction conditions; the formation of 2-substituted quinolines was not noticed. 3-Cyanoquinoline N-oxide (**1g**) gave only the 2-substituted quinoline (**3g**) under both the reaction conditions.

Furthermore, isoquinoline 2-oxide (**7**) reacted readily with **2** under different conditions to give always the 1-substituted isoquinoline (**8**).

No satisfactory results were obtained with pyridine N-oxide; only 5-dimethylaminomethylene-2-thiobarbituric acid (**9**) was obtained when pyridine N-oxide was treated with **2** in Ac_2O (1.2 eq.)-DMF at room temperature for 8 hr.

The formation of **3** and **4** from **1** can be well explained by a mechanism shown in Scheme 1. Formation of **3** involves a 1,2-dihydroquinoline intermediate (**A**), which loses a molecule of acetic acid to give the product (Path-a). According to the mechanism previously proposed for N-ylide formation from quinoline N-oxides and some active methylenes[6], the formation of N-ylide (**4**) should be assumed to follow path-b which proceeds through an aziridine intermediate (**B**). However the intermediacy of **B** seems rather unlikely in this case because of its highly strained structure. This situation suggests the possibility of alternative path-c, which involves the N-OAc bond fission followed by concerted 1,2-shift of the side chain in **A**.



Scheme 1

Reaction of quinoline 1*-oxides* (**1a-d**) *with* 2*-thiobarbituric acid* (**2**)

Method-A

A solution of **1** (0.011 mol) and acetic anhydride (8 ml) was added to a solution of **2** (0.01 mol) in acetic anhydride (5 ml) and the reaction mixture heated at 90°. The reactants immediately turned orange with the appearance of orange precipitate. The heating was continued for 2 hr when the precipitation had ceased the precipitate was filtered and recrystallized from acetic acid to give **3** as orange granules (Table 1). The spectral data of **3** are given in Table 2.

Method-B

A solution of **1** (0.01 mol) in DMF (5 ml) and acetic anhydride (1.2 ml) was added in one lot to a solution of **2** (0.01 mol) in DMF (5 ml) and the reaction mixture heated at 90°. Fine crystals began to separate after 10 min. Heating at 90° was continued for 2 hr when the precipitation had ceased. The precipitate was filtered and recrystallized from acetic acid to give **4** (Table 1). The spectral data of **4** are given in Table 2.

Table 1—Reaction of Quinoline N-Oxides (**1a-h**) with 2-Thiobarbituric Acid (**2**)

N-Oxide	Medium/temp. (°C)	Reaction period (hr)	Product* (yields %)		Mol. formula	N (%)†	
						Found	Calc.
1a	Ac_2O-DMF/90°	3	—	4a(93)	$C_{13}H_{13}N_3O_4S$	13.7	(13.7)
	Ac_2O/90°	2	3a(84)	—	$C_{13}G_{11}N_3O_3S$	14.3	(14.5)
1b	Ac_2O-DMF/90°	1	—	4b	$C_{14}H_{15}N_3O_4S$	13.0	(13.1)
	Ac_2O/90°	2	3b(88)	—	$C_{14}H_{13}N_3O_3S$	13.0	(13.1)
1c	Ac_2O-DMF/90°		—	4c(87)	$C_{13}H_{12}N_3O_4ClS$	10.2	(10.7)
	Ac_2O/90°	2	3c(87)	—	$C_{13}H_{10}N_3O_3ClS$	13.1	(13.0)
	Ac_2O/90°	2	3c(87)	—	$C_{13}H_{10}N_3O_3Cls$	13.1	(13.0)
1d	Ac_2O-DMF/90°	4	—	4d(88)	$C_{14}H_{15}N_3O_5S$	12.2	(12.5)
	Ac_2O/90°	2	3d(80)	—	$C_{14}H_{13}N_3O_4S$	13.1	(13.2)
1e	Ac_2O-DMF/90°	3	—	4e(88)	$C_{17}H_{20}N_4O_5S$	14.6	(10.8)
	Ac_2O/90°	2	—	4e(81)			
1f	Ac_2O-DMF/90°	2	—	4f(87)	$C_{13}H_{12}N_3O_4BrS$	11.7	(10.8)
	Ac_2O/90°		-	4(84)			
1g	Ac_2O-DMF/90°		3g(80)	—	$C_{14}H_{10}N_4O_3S$	16.8	(17.9)
	Ac_2O/90°		3g(83)	—			

*All the products obtained had m.p. above 300°.
†Satisfactory C, H analysis were obtained for all the products.

Table 2—Spectral Data of 5-(2-Quinolyl)-2-thiobarbituric Acids (**3**) and Quinolinium-N-5-(2-thio)barbituric Acid Yields (**4**)

Compd*	UV (log ε), ethanol, nm	PMR (DMSO-d_6), ppm					
		C_2-H	C_3-H	C_4-H	Ar-H	NH†	Others
3a	234 (3.9), 282 (3.2) 386 (3.8)	—	9.15 (1H, *d*, *J*= 10 Hz)	8.45 (1H, *d*, *J*= 10 Hz)	7.5-8.2 4.5H, m)	10.95 (2H, *bs*) 16.5 (0.5H, *bs*)	
3b	213 (4.5), 241 (4.6) 289 (3.9), 395 (3.9)	—	9.01 (1H, *s*)	—	7.4-8.5 (4.9H, m)	10.0 (1H, *bs*) 10.21 (1H, *bs*) 16.21 (0.1H, *bs*)	2.7 (3H, *s*, Me)
3c	222 (4.5), 249 (4.3), 282 (4.4), 374 (4.3)	—	9.32 (1H, *s*)	—	7.56-8.1 (4H, *m*)	10.0 (2H, *bs*) 16.26 (1H, *bs*)	
3d	219 (4.9), 249 (4.3), 282 (4.4), 374 (4.3)	—	8.72 (1H, *s*)	—	7.4-8.05 4.9H, *m*)	16.6 (2H, *bs*,) 15.06 (1H, *bs*)	4.08 (3H, *s*, OMe)
3e	220 (4.8), 248 (4.2), 280 (4.3), 375 (4.3)	—	—	—	7.9-8.5 (5.5H, *m*)	10.0 (1H, *bs*) 10.15 (1H, *bs*) 12,09 (0.5H, *bs*)	
4a	209 (3.8), 263 (4.1), 318 (3.7)	9.2 (1H, *m*)	9.3 (1H, *m*)	—	7.6-8.43 (5H, *m*, containing C_4-H)	10.15 (2H, *bs*)	
4b	205 (4.4), 230 (4.5), 320 (3.8)	9.0 (1H, *d*, *J*= 10 Hz)	8.05 (1H, *d*, *J*= 10 Hz)	—	7.8-8.1 (3H, *m*) 8.45 (1H, *dd*, *J*= 11 Hz, 2Hz, C_8-H)	10.0 (2H, *bs*)	3.0 (3H, *s*, Me)
4c	230 (4.5), 300 (4.5), 365 (3.9)	8.55 (1H, *d*, *J*= 8 Hz)	7.09 (1H, *d*, *J*= 8 Hz)	—	7.6-8.04 (4H, *m*)	10.2 (2H, *bs*)	
4d	212 (4.5), 245 (4.5), 320 (4.2)	9.07 (1H, *d*, *J*= 8 Hz)	8.01 (1H, *d*, *J*= 8 Hz)	—	7.73-8.12 (4H, *m*)	9.85 (2H, *bs*)	4.31 (3H, *s*, OMe)
4e	210 (4.0), 250 (4.1) 364 (4.0)	8.5	7.1	—	7.6-8.02	9.85 (1H, *bs*) 9.99 (1H, *bs*)	3.3 (4H, *t*, *J*= 4 Hz, CH_2NCH_2) 3.84 (4H, *t*, *J*= 4 Hz, CH_2OCH_2)
4f	210 (4.2), 250 (4.0), 363 (4.0)	9.1 (1H, *s*)	—	—	7.6-8.1 (5H, *m*, containing C_4-H)	10.0 (2H, *bs*)	

*IR = 3100-3200 (NH), 1720-1735 cm^{-1} (CO).
†Exchangeable with D_2O.

Method-C

A solution of **1** (0.01 mol) in acetic anhydride (1.2 ml) and DMF (7 ml) was added dropwise to a solution of **2** (0.01 mol) in DMF (5 ml) at room temperature. Fine yellow crystals gradually separated out. After 3 hr, the precipitated crystals were filtered and recrystallized from 5% hydrochloric acid to afford **4** as yellow needless (Table 1).

Oxidation of **3a** *with hydrogen peroxide in acetic acid*

A mixture of **3a** (0.01 mol) and hydrogen peroxide (30 ml, 30%) in acetic acid (30 ml) was refluxed for 4 hr, and the solution concentrated under reduced pressure. The colourless residue was recrystallized from ethanol to give **5** in 68% yield; gave colourless prisms from ethanol-methanol, m.p. 295° (d); IR (nujol): 1725, 1755 (CO), 3200 cm^{-1} (NH); PMR (DMSO-d_6): δ 7.62-7.92 (3H, *m*, Ar-*H*), 8.1 (1H, *d*, *J*= 9 Hz, C_3- or C_4-H), 8.14 (1H, *d*, *J*= 9 Hz, C_3- or C_4-H); 8.35 (1H, *d*, *J*= 8.5 Hz, C_8-H), 8.37 (1H, *s*, >CH−), 11.5 (2H, *s*, NH).

Oxidation of **4a** *to quinoline-1-oxide* (**1a**)

A mixture of **4a** (0.01 mol) and hydrogen peroxide (35 ml, 30%) in acetic acid (35 ml) was refluxed for 7 hr to give an almost colourless solution. The solution was concentrated under reduced pressure to give **1a** in 76% yield, identified by direct comparison (m.m.b.) with an authentic sample.

Reaction of 4-chloroquinoline with thiobarbituric acid **2**

Anhyd. DMF (7 ml) was added through a dropping funnel to 1 g of 50% sodium hydride (0.22 mol) placed in a three necked flask. The reaction flask was placed in an ice-bath while compound **2** (0.01 mol) in anhydrous DMF (7 ml) added to it dropwise. Af-

ter the addition was complete, the ice-bath was replaced by an oil-bath. The reaction mixture was heated to 50° to 4-chloroquinoline (1.6 g, 0.01 mol) in DMF added to it dropwise. The reaction temperature was raised slowly to 120° and maintained at this temperature for 5 hr. The reaction mixture was cooled and acetic acid (5 ml) added. The separated yellow crystals were filtered and recrystallized from acetic acid to give **6** in 80% yield,m.p. > 300°; IR: 1720 (CO), 3200 cm^{-1} (NH); PMR: δ 8.7 (1H, *d*, *J*= 8 Hz, C_2-H), 7.0 (1H, *d*, *J*= 8 Hz, C_3-H), 7.5-8.0 (4H, *m*, Ar-*H*), 11.1 (2H, *s*, NH).

Reaction of 4-*morpholino- and* 3-*bromoquinoline* 1-*oxides* (**1e, f**) *with* **2**

A solution of **1e, f** (0.01 mol) in acetic anhydride (7 ml) was added to a solution of **2** (0.01 mol) in acetic anhydride (13 ml) and the reaction mixture heated at 90° for 3 hr. The precipitated orange crystals were filtered and recrystallized from acetic acid to give **4e, f** (Table 1; method-**A**).

Same results were obtained when the reaction was repeated using method B or C. Similarly the reaction of 3-cyanoquinoline-1-oxide (**1g**) with **2**, using method A, B or C gave **3g** (Table 1).

Reaction of isoquinoline-2-*oxide* (**7**) *with* **2**

Compound **7** reacted readily with **2** under various reaction conditions (method A, B or C) to give the 1-substituted isoquinoline **8** in 76% yield, m.p. > 300°; IR: 1720 (CO), 3180 cm^{-1} (NH): PMR; δ 7.6-8.3 (7H, *m*, Ar-*H* and $\widetilde{>}$CH−), 9.0 (2H, *brs*, NH).

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Isomerization of Homoallyl Alcohols over Raney Nickel

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Homoallyl alcohols undergo ready isomerization to the corresponding aldehydes or ketones when refluxed in a solvent with Raney nickel. Reaction pathways, based on identification of intermediates of the reactions, involve dehydrogenation-hydrogenation for the cyclic alcohols and double bond shift for the open chain alcohols.

Allyl alcohols undergo isomerization in the presence of Raney nickel to the corresponding carbonyl compounds either by a 1,3-sigmatropic shift of hydrogen[1] or by hydrogen atom addition and elimination via a σ-alkyl complex ('half-hydrogenated species')[2]. Homoallyl alcohols also undergo isomerization under similar conditions (e.g. cholesterol → cholestanone)[3,4] in the presence of Raney nickel. However, substrates other than cholesterol do not seem to have been examined. Presently we have studied the isomerization, in the presence of Raney nickel, of the following homoallyl alcohols: but-3-en-1-ol (**1**), cyclohex-3-en-1-ol (**2**), *endo*- and *exo*-bicyclo[2.2.1]hept-5-en-2-ols (**3** and **4**) and cholesterol (**5**).

Isomerization of **1** and **2** in the presence of other catalysts has been reported[5-8]. Isomerization of **3** and **4** has not been reported so far.

The isomerizations were carried out by refluxing the substrate with Raney nickel[1] in the present of a solvent (methanol in the case of **1** and xylene in the case of **2** and **5**). Samples were withdrawn periodically and analyzed by gas chromatography in the case of volatile substrates (**1** to **4**) and by column chromatography in the case of **5**. Wherever necessary the products were isolated by preparative chromatography and identified by IR and PMR spectroscopy. The results are presented in Tables 1 to 4.

The products of isomerization were butanal from **1**, cyclohexanone from **2**, bicyclo[2.2.1]heptan-2-one from **3** and **4** and cholestanone and coprastanone from **5**. In addition small quantities of the saturated alcohols corresponding to the hydrogenation of the final carbonyl compounds were also detected. It was also noted that the amounts of intermediates increased initially and then decreased as the reaction progressed. No gas (H_2) evolution was noticed in any of the reactions showing that if there was an initial dehydrogenation the hydrogen so produced was retained by the catalyst till it was used up for the hydrogenation of the unsaturated substrates.

But-3-en-1-ol (**1**) was much more reactive than any of the cyclic alcohols and the isomerization pro-

Table 1—Isomerization of But-3-en-1-ol (**1**) over Raney Nickel

[Catalyst to substrate ratio (wt/wt): 0.25; temp. = 64°C; weight of **1** used = 5 g]

Sl No.	Reaction time (hr)	Product distribution (mol %)		
		Crotyl alcohol	Butanal	Butanol
1	0.5	8	4	traces
2	1.0	15	11	traces
3	1.5	20	14	2
4	2.0	21	25	3
5	3.0	15	30	4
6	6.0	10	44	6

Table 2—Isomerization of Cyclohex-3-en-1-ol (**2**) over Raney Nickel

[Catalyst to substrate ratio (wt/wt): 0.25; temp. = 135-40°C; weight of **2** taken = 5 g]

Sl No.	Reaction time (hr)	Product distribution (mol %)		
		Cyclohex-2-en-1-one	Cyclohexanone	Cyclohexanol
1	6	15	5	3
2	12	29	18	5
3	18	20	25	9
4	24	17	40	12

Table 3—Isomerization of Bicyclo[2.2.1]hept-5-en-2-ol (**3** and **4**) over Raney Nickel[a]

[Catalyst to substrate ratio (wt/wt): 0.25; temp. = 135-40°C; Amount of substrate taken = 3 g]

Sl No.	Reaction time (hr)	Product distribution (mol %)	
		Bicyclo[2.2.1]-heptan-2-one	Bicyclo[2.2.1]-heptan-2-ol
1	12	10	4
2	24	28	5
3	36	42	7
4	48	53	7
5	24	32	4
6	24	30	5

[a]For Sl Nos 1-4 starting material was *endo*- and *exo*-mixture in the ratio of 2:1. For Sl Nos 5 and 6 *endo*- and *exo*-alcohols, respectively were used.

Table 4—Isomerization of Cholesterol over Raney Nickel

[Catalyst to substrate ratio (wt/wt): 0.25; temp. = 135-40°C; Amount of substrate taken = 1 g]

Sl No.	Reaction time (hr)	Product distribution (mol %)[a]	
		Δ^4-Cholestanone	Cholestanone
1	1	30	traces
2	4	60	7
3	10	15	68
4[b]	1	28	9[c]
5[b]	4	40	20

[a]Yields based on products separated by column chromatography.
[b]Epicholesterol was used.
[c]Coprostanone: cholestanone = 1:1 was obtained.

gressed rapidly at 64°C (methanol solution) to give butanal along with small quantities of butanol as the final products. The two possible reaction sequences are shown in Eqs (1) and (2).

1 → crotyl alcohol → enol of butanal → butanal ...(1)

$$\mathbf{1} \xrightarrow{-2H} \text{crotanaldehyde} \xrightarrow{+2H} \text{butanal} \qquad \ldots(2)$$

The only intermediate detected during the progress of the reaction was crotyl alcohol which increased in concentration and reached a maximum in 2 hr and then the concentration decreased. The product formation through Eq. (2) appears unlikely since α,β-unsaturated aldehydes and ketones are readily hydrogenated to the saturated aldehydes and ketones rather than to the unsaturated alcohols. Hence isomerization of **1** occurs via Eq. (1). The double bond shifts are most probably through the 'half-hydrogenated species' as already reported for substituted allyl alcohols[2].

Cyclohex-3-en-1-ol (**2**) undergoes isomerization very slowly at the reflux temperature of methanol. Even in xylene (b.p. 135-40°C) the reaction was much slower than that of **1**. Cyclohex-2-en-1-one was clearly observed as an intermediate and the possible reaction sequence is shown in Eq. (3).

$$\text{Cyclohex-3-en-1-ol} \xrightarrow{-2H} [\text{cyclohex-3-en-1-one}] \rightarrow \text{Cyclohex-2-en-1-one} \xrightarrow{+2H} \text{cyclohexanone} \qquad \ldots(3)$$

The initially formed intermediate, cyclohexa-3-en-1-one was not detected. This intermediate seems to have undergone rapid isomerization to the conjugated unsaturated ketone.

endo- and *exo*-Bicyclo[2.2.1]hept-5-en-2-ols (**3** and **4**) gave bicyclo[2.2.1]heptan-2-one and no intermediate could be detected. The *endo*- and the *exo*-alcohols reacted at the same rate showing that direct intra or intermolecular hydrogen transfer was not happening. Since double bond shifts are not possible in this system the course of reaction must involve the steps outlined the Eq. (4).

$$\mathbf{3} \text{ or } \mathbf{4} \xrightarrow{-2H} \text{bicyclo[2.2.1]hept-5-en-2-one} \xrightarrow{+2H} \text{bicyclo[2.2.1]heptan-2-one} \qquad \ldots(4)$$

The non-detection of the intermediate unsaturated ketone was due to its rapid hydrogenation to the saturated ketone, which was independently verified. This high reactivity is understandable in view of the relief of strain obtained on the hydrogenation of this strained double bond.

As reported by earlier workers[3] cholesterol underwent ready isomerization to cholestanone and the intermediate Δ^4-cholestenone could be readily identified. Coprostanol was detected only in one experiment at low concentration. The reaction sequence as earlier suggested[3], is valid (see Eq. 5).

$$\mathbf{5} \xrightarrow{-2H} [\Delta^5\text{-cholestenone}] \rightarrow \Delta^4\text{-cholestenone} \xrightarrow{+2H} \text{cholestanone}(+\text{coprostanone}) \qquad \ldots(5)$$

Coprostanone itself is known to isomerize to cholstanone under the experimental conditions[3].

The results presented above indicate that in the case of cyclic homoallyl alcohols, initial dehydrogenation to the unsaturated ketone takes place. The β,γ-unsaturated ketone, if the structure permits, rapidly isomerizes to the α,β-unsaturated ketone which is then hydrogenated to the saturated ketone. The hydrogen formed in the initial dehydrogenation step is not released as molecular hydrogen, but is retained by the catalyst till it is used up in the second hydrogenation step. In the case of but-3-en-1-ol (**1**) there is no evidence for an initial dehydrogenation and the isomerization seems to involve two successive double bond shifts to form the enol of butanal.

Thanks are due to the RSIC, IIT, Madras for the spectra.

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Synthesis & Fungitoxicity of New 1,3,4-Oxadiazolo[3,2-*a*]-*s*-triazine-5,7-diones & Their Thione Analogues

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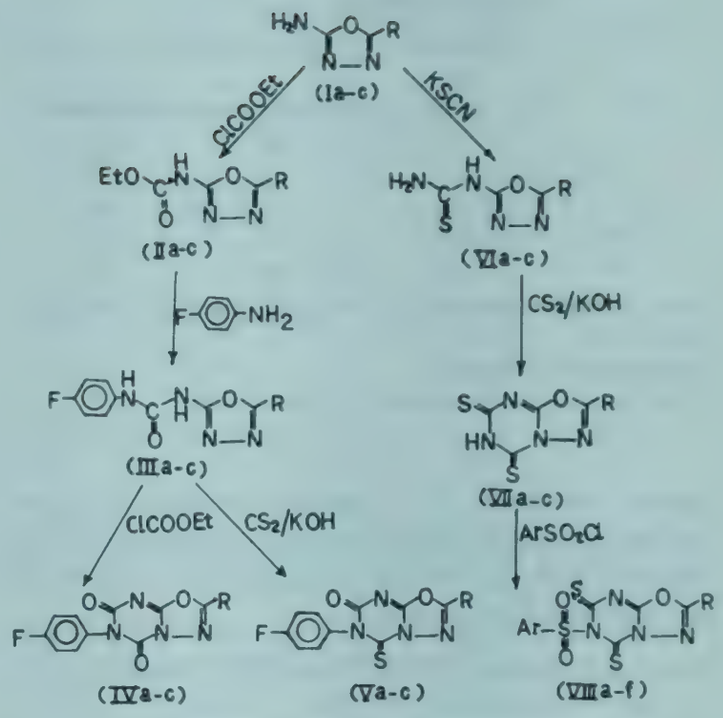
N^1-(5-Aryl-1,3,4-oxadiazol-2-yl)-N^3-(4-fluorophenyl)ureas (IIIa-c) on cyclocondensation with ethyl chloroformate and CS_2/KOH afford 2-aryl-6-(4-fluorophenyl)-1,3,4-oxadiazolo[3,2-*a*]-*s*-triazine-5,7-diones (IVa-c) and their 5-thione analogues, respectively. 6-Fluoroarenesulphonyl derivatives (VIIIa-f) are obtained by treating VIIa-c, the condensation products of oxadiazolylthioureas (VIa-c) and CS_2/KOH, with arenesulphonyl chlorides. The compounds III-VIII have been compared with Dithane M-45 for their fungitoxic action against *A. niger* and *F. oxysporium*, and the results correlated with their structural features.



Scheme 1

Previously, we have reported[1-4] the synthesis and fungicidal activity of 1,3,4-oxa(thia)diazolo[3,2-*a*]-*s*-triazine-thiones incorporating the thione function either at position 5 or 7. The significant fungitoxicity displayed by some of these compounds, prompted us to synthesise more compounds of this class with certain structural modifications. The synthesis and evaluation of fungicidal activity of 1,3,4-oxadiazolo[3,2-*a*]-*s*-thiazine-5,7-diones and their thione analogues are described in this note. The presence of a fluoroaryl or fluoroarenesulphonyl moiety in these compounds is expected to enhance their fungicidal action.

1,3,4-Oxadiazolo[3,2-*a*]-*s*-triazine-5,7-diones (IVa-c) and their 5-thione analogues (Va-c) were synthesised by the cyclocondensation of the corresponding ureas (IIIa-c) with ethyl chloroformate and CS_2/KOH, respectively (Scheme 1). Similar condensation of oxadiazlylthioureas (VIa-c) with CS_2/KOH furnished the oxadiazolo-*s*-triazine-5,7-dithiones (VIIa-c) which were treated with arenesulphonyl chlorides to yield the corresponding sulphonylated products (VIIIa-f). The required ureas (IIIa-c) were prepared by reacting 2-aminooxadiazoles (Ia-c) with ethyl chloroformate followed by treatment with 4-fluoroaniline. Similarly, oxadiazolylthioureas (VIa-c) were obtained[5] by the action of KSCN on 2-amino-5-aryl-1,3,4-oxadiazoles (Ia-c) which in turn were obtained by oxidative cyclisation of the aldehyde semicarbazones following the method of Gibson[6].

The structural assignments of all the synthesised compounds were based on elemental analyses, and IR and PMR spectral data. The spectral data of only the representative compounds are given in Table 1.

Fungicidal screening

The fungicidal activity was evaluated against *Aspergillus niger* and *Fusarium oxysporium* by the usual agar-plate technique[7] at 1000, 100 and 10 ppm concentrations using Dithane M-45 as standard. The antifungal activity of the compounds III-VIII is given in Table 2. Among these, compounds IVb, Vb, c, VIIb and VIIIb exhibited fungitoxicity of the order of Dithane M-45 at 1000 ppm concentration against both the test fungi.

A comparison of the fungitoxic data of IVa-c with those of Va-c clearly indicates that the latter containing $>C=O$ and $>C=S$ functions are more active than the former incorporating only $>C=O$ groups. This is in coformity with the earlier observation that the combination of $>C=O$ and $>C=S$ functions sometimes works better than either alone[8]. In general, compounds IVa-c, Va-c and VIIa-c are more potent than their parent ureas (IIIa-c) and thioureas (VIa-c). This may be attributed to the more planar and compact structure[1,9-11] of these condensed he-

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Table 1 — Characterization Data of Various Compounds Prepared

Compd	R	Ar	Yield (%)	m.p. °C	Mol. formula	Found (%) (Calc.)			
						C	H	N	
IIa*	C_6H_5	—	75	205-7	$C_{11}H_{11}N_3O_3$	56.5	4.7	17.9	—
						(56.7	4.7	18.0	—)
IIb	*p*-Cl.C_6H_4	—	81	206-8	$C_{10}H_{10}ClN_3O_3$	49.2	3.7	15.5	—
						(49.4	3.7	15.7	—)
IIc	*p*-CH_3O.C_6H_4	—	84	235-37	$C_{12}H_{13}N_3O_4$	54.5	4.8	15.8	—
						(54.8	4.9	16.0	—)
IIIa†	C_6H_5	—	59	230-31	$C_{15}H_{11}FN_4O_2$	60.2	3.9	18.6	—
						(60.4	3.7	18.8	—)
IIIb	*p*-Cl.C_6H_4	—	67	225-27	$C_{15}H_{10}ClFN_4O_2$	54.4	3.1	16.9	—
						(54.1	3.0	16.8	—)
IIIc	*p*-CH_3O.C_6H_4	—	61	252	$C_{16}H_{13}FN_4O_3$	58.4	4.0	16.9	—
						(58.5	4.0	17.1	—)
IVa‡	C_6H_5	—	69	241	$C_{16}H_9FN_4O_3$	59.1	2.6	17.1	—
						(59.3	2.8	17.3	—)
IVb	*p*-Cl.C_6H_4	—	78	250-51	$C_{16}H_8ClFN_4O_3$	53.5	2.2	15.6	—
						(53.6	2.3	15.6	—)
IVc	*p*-CH_3O.C_6H_4	—	73	246	$C_{17}H_{11}FN_4O_4$	57.6	3.1	15.7	—
						(57.6	3.1	15.8	—)
Va**	C_6H_5	—	76	215-17	$C_{16}H_9FN_4O_2S$	56.6	2.5	16.4	9.4
						(56.5	2.6	16.5	9.4)
Vb	*p*-Cl.C_6H_4	—	82	198	$C_{16}H_8ClFN_4O_2S$	51.1	2.3	14.8	8.5
						(51.3	2.1	15.0	8.5)
Vc	*p*-CH_3O.C_6H_4	—	86	228-29	$C_{17}H_{11}FN_4O_3S$	55.4	3.1	15.1	8.5
						(55.1	3.0	15.1	8.6)
VIIa§	C_6H_5	—	82	230	$C_{10}H_6N_4OS_2$	46.0	2.4	21.4	24.4
						(45.8	2.3	21.4	24.4)
VIIb	*p*-Cl.C_6H_4	—	85	205-6	$C_{10}H_5ClN_4OS_2$	40.4	1.9	18.7	21.4
						(40.5	1.7	18.9	21.6)
VIIc	*p*-CH_3O.C_6H_4	—	84	232	$C_{11}H_8N_4O_2S_2$	45.3	2.9	19.1	21.8
						(45.2	2.7	19.1	21.9)
VIIIa	C_6H_5	4-F-C_6H_5	71	165-66	$C_{16}H_9FN_4O_3S_3$	45.8	2.2	13.4	—
						(45.7	2.1	13.3	—)
VIIIb	*p*-ClC_6H_4	4-F-C_6H_5	82	182	$C_{16}H_8ClFN_4O_3S_3$	42.0	1.8	12.2	—
						(42.2	1.8	12.3	—)
VIIIc††	*p*-CH_3O.C_6H_4	4-F-C_6H_5	78	215-17	$C_{17}H_{11}FN_4O_4S_3$	45.1	2.3	12.5	—
						(45.3	2.4	12.4	—)
VIIId	C_6H_5	5-F-2-CH_3-C_6H_3	66	195-97	$C_{17}H_{11}FN_4O_3S_3$	46.8	2.4	12.8	—
						(47.0	2.5	12.9	—)
VIIIe	*p*-Cl.C_6H_4	5-F-2-CH_3-C_6H_3	69	212-14	$C_{17}H_{10}ClFN_4O_3S_3$	43.6	2.2	11.9	—
						(43.5	2.1	12.0	—)
VIIIf	*p*-CH_3O.C_6H_4	5-F-2-CH_3-C_6H_3	73	120	$C_{18}H_{13}FN_4O_4S_3$	46.4	2.9	12.2	—
						(46.6	2.8	12.1	—)

*IR = 1730 cm^{-1} (C=O).
†IR = 3290 (N−H), 1660 cm^{-1} (C=O).
‡IR = 1705 cm^{-1} (C=O); PMR = δ 7.00-8.10 (*m*, 9H, Ar-*H*).
**IR = 1695 (C=O), 1090 cm^{-1} (C=S); PMR: δ 7.00-8.10 (*m*, 9H, Ar-*H*).
§IR = 3120 (N−H), 1080 cm^{-1} (C=S).).
††IR = 1100 (C=S), 1155, 1330 cm^{-1} (SO_2); PMR = δ 3.80 (*s*, 3H, OCH_3), 7.00-8.22 (*m*, 8H, Ar-*H*).
‡IR = 1090 (C=S), 1160, 1355 cm^{-1} (SO_2); PMR = δ 2.38 (*s*, 3H, CH_3), 7.04-8.00 (*m*, 7H, Ar-*H*).

terocycles than their precursors, as well as to the presence of an additional >C=O or >C=S group[8].

M.ps were determined in open capillaries and are uncorrected. IR spectra in KBr were recorded on a Hitachi-295 infrared spectrophotometer, and PMR spectra in DMSO-d_6 on a 60 MHz Varian EM 360L spectrometer using TMS as internal standard. The spectral data of only representative compounds are given in Table 1. 2-Amino-5-aryl-1,3,4-oxadiazoles (Ia-c)[6,12] were prepared by oxidative cyclisation of aldehyde semicarbazones with bromine in gl. acetic acid in the presence of anhyd. sodium acetate.

Table 2 — Fungicidal Screening Results of the Compounds III-VIII

Compd	Inhibition (%) against					
	A. niger at			*F. oxysporium* at		
	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
IIIa	61	31	18	60	29	17
IIIb	68	39	22	66	36	19
IIIc	67	37	21	60	33	17
IVa	81	39	29	79	39	27
IVb	98	50	40	96	48	38
IVc	90	49	36	89	47	35
Va	86	53	45	85	50	43
Vb	100	70	53	99	68	52
Vc	100	62	46	98	61	44
VIa	52	29	11	50	26	9
VIb	57	30	16	54	25	13
VIc	55	29	14	53	25	12
VIIa	85	53	32	82	51	31
VIIb	99	61	42	99	58	41
VIIc	90	57	38	88	53	35
VIIIa	88	57	35	85	54	34
VIIIb	100	65	52	99	63	50
VIIIc	93	59	42	90	55	37
VIIId	86	54	34	84	52	32
VIIIe	97	62	45	92	60	41
VIIIf	92	58	40	89	55	36
Dithane M-45	100	81	67	100	85	68

Ethyl N-(5-aryl-1,3,4-oxadiazol-2-yl)carbamates (IIa-c; Table 1)

To Ia (6.44 g, 0.04 mol) in pyridine (160 ml) were added ethyl chloroformate (4.78 g, 0.044 mol) and triethylamine (10 ml) and the mixture was refluxed for 1 hr, poured into dil. HCl (320 ml, 50%, v/v), and the carbamate (IIa) thus obtained recrystallised from ethanol. In a similar way IIb and IIc were prepared and recrystallised from ethanol.

N^1-(5-Aryl-1,3,4-oxadiazol-2-yl)-N^3-(4-fluorophenyl)ureas (IIIa-c; Table 1)

An equimolar mixture of II and 4-fluoroaniline in ethanol was refluxed for 16 hr, the solvent distilled and the residue washed with water and recrystallised from ethanol to furnish III.

2-Aryl-6-(4-fluorophenyl)-1,3,4-oxadiazolo[3,2-a]-s-triazine-5,7-diones (IVa-c; Table 1)

To a solution of III (0.01 mol) in pyridine (40 ml) was added ethyl chloroformate in an ice-bath. The mixture was stirred at room temperature for 2 hr, then refluxed for 1 hr, treated with 1 *N* KOH (40 ml) and the product thus precipitated recrystallised from ethanol to give IV.

2-Aryl-6-(4-fluorophenyl)-5-thioxo-1,3,4-oxadiazolo[3,2-a]-s-triazine-7-ones (Va-c; Table 1)

A mixture of III (0.01 mol), ethanol (40 ml) and carbon disulphide (1.52 g, 0.02 mol) was refluxed for 6 hr, concentrated to a small volume, poured into ice-cold water, acidified with dil. HCl and the precipitated product (V) recrystallized from ethanol.

N^1-(5-Aryl-1,3,4-oxadiazol-2-yl)thioureas (VIa-c)

These were prepared following the method of Viswanathan *et al.*[5]. All the three oxadiazolylthioureas (VIa-c) are already reported in literature[13].

2-Aryl-1,3,4-oxadiazolo[3,2-a]-s-triazine-5,7-(6H)-dithiones (VIIa-c; Table 1)

These were prepared employing the same procedure as described for V using thioureas (VIa-c) in place of ureas (IIIa-c), and recrystallised from ethanol.

2-Aryl-6-arenesulphonyl-1,3,4-oxadiazolo[3,2-a]-s-triazine-5,7-dithiones (VIIIa-f; Table 1)

A mixture of VII (0.01 mol), and an appropriate arenesulphonyl chloride (0.01 mol) in freshly distilled pyridine (10 ml) was heated at 100° for 1-1.5 hr, poured into excess of dil. HCl, and the precipitated product recrystallised from ethanol to give VIII.

The authors are thankful to Prof. S C Tripathi for providing laboratory facilities, and to Dr R K Khare, City University of New York, USA for elemental analyses and IR and PMR spectra. One of them (A R M) is thankful to UGC, New Delhi for the award of a teacher fellowship under faculty improvement programme.

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BOOK REVIEWS

Medicinal Plants of India: Vol. 2, edited by G V Satyavati, Ashok K Gupta, Neeraj Tandon (neé Bhatia) & S D Seth (Indian Council of Medical Research, New Delhi), 1987, pp. xi + 600. Price Rs 136.00; $ 33; £ 20.

This comprehensive compendium is second in the series on medicinal plants of India. The first compendium was brought out nearly a decade ago and was dedicated to Prof T R Seshadri. The present volume is dedicated to Dr C Dwarkanath, New Delhi, who has made outstanding contributions to traditional medicine. The first volume gave scientific information on over 350 botanical species presented in the alphabetical order A to G. The present volume gives published information on over 550 taxa arranged alphabetically (H to P) covered in 600 pages.

In this volume serious efforts have been made on scientific evaluation of medicinal plants, and a disease-oriented approach to research on traditional medicine has been adopted, instead of drug-oriented approach. This would be more useful and appealing to the researchers in this area and also to the readers.

This compendium deals with Indian medicinal plants, their vernacular names, traditional uses, botanical characteristics and their present chemical and pharmacological status. Twelve genera which have been documented, cover different families of the monocotyledonae and dicotyledoneae.

The book is well written and the material is lucidly presented. However, under the title of each genus a few species have been described in the text with their scientific names in capital letters. This is unacceptable according to the principle of taxonomy.

The bibliography provided mostly includes the works of the Indian authors. In connection with the biological screening of plants references of only Indian authors have been cited but those of foreign authors like Norman R Farnsworth, Albert Hofmann, Ara H Marderosian and others who have carried out brilliant investigations are found missing. An important plant species—*Ipomoea violaceae*, which is known as Morning Glory and grown in gardens has not been included. The seeds of this plant yield ergot alkaloids which provided for the first time an example of the occurrence of ergot alkaloids in higher plants. *Lathyrus* (Leguminosae) genus has been totally omitted in the book. *Lathyrus sativus* Linn. containing active principles which cause lathyrism is widely cultivated as pulse in our country. Chemical and pharmacological studies of its seeds have been carried out. *Punica granatum* Linn. has been discussed at the end (pp 539-544) but the presence of pelletierine alkaloids (piperidine group) detected in the bark by Tanret in 1877 and named in honour of the French chemist-P Joseph Pellitier, has not been mentioned. The pomegranate alkaloids are used as anthelmintics.

Last but not the least the reviewer fails to understand why the editors have made no mention about marine plants which yield useful pharmaceuticals and biodynamic principles. The coloured photoplates of the plants included in this volume are really praiseworthy and well labelled.

The Council deserves deep appreciation for the collection of documents scattered far and wide and for this comprehensive compilation.

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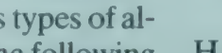
Solvomercuration/Demercuration Reactions in Organic Synthesis by R C Larock (Springer-Verlag, Heidelberg), 1986, pp. XIII + 607, Price 485 DM.

As the author states in the preface, this monograph is intended to cover the valuable solvomercuration-demercuration reactions in detail that organometallic and synthetic organic chemists would find desirable. In fact, the author, a prominent figure in the discipline, has managed to pull together in a remarkably comprehensive fashion a most readable and authoritative account of the subject, incorporating all the major works and reviews in the field covering the chemical literature through mid 1983.

The monograph is divided into 13 chapters including an introduction (Chapter I) and an excellent subject index, and 40 'Organic Reactions' type comprehensive tables focussing on synthetically useful transformations giving reagents, essential conditions and representative yields. Chapter I gives a few important earlier reviews on this subject. Through Chapters II to

V are discussed in depth hydroxymercuration, alkoxymercuration, peroxymercuration and acyloxymercuration reactions respectively in various types of alkenes, alkynes and their derivatives. In the following four chapters aminomercuration, amidomercuration, azidomercuration and nitromercuration are discussed. The applications of solvomercuration products for free radical additions to alkenes and intramolecular carbon-carbon bond formation in polyenes which represent some of the important developments in the recent years in synthetic chemistry, have been focussed in depth in Chapter X. The following two Chapters incorporate halomercuration and miscellaneous mercuration reactions.

The book is well printed and the formulae are exceptionally clear. A few minor, readily recognizable and easily corrected errors were found; for example, in Table 2.2 (p. 19) last entry of alkene should be



and in Table 2.3 (p. 48) the structure of the alkene in entry No. 5 is missing.

In summary, this monograph deals with every aspect of synthetic applications of solvomercuration-demercuration reactions with a remarkable wealth of details and will be very useful to everyone with an interest in this field as an easy reference book.

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ANNOUNCEMENTS

IUPAC Recommendations on Nomenclature for Organic Chemical Transformations

These rules provide a general system of nomenclature for transformations whereby one organic compound is converted into another. A *transformation* is distinct from a *reaction* in that it describes only those changes that are involved in converting the structure of a substrate into that of a product, regardless of the reagent or the precise nature of the substrate, or (with some exceptions) the mechanism. Thus all processes in which $X-H$ is converted into $X-NO_2$ are examples of the single transformation called 'nitration', whatever the nature of X, and irrespective of whether the reaction entails the replacement of H^+ by NO_2^+, of $H^\cdot$ by $NO_2^\cdot$, or of H^- by NO_2^-.

The basis of the names of all transformations is that they provide a description of the conversion of substrate into product by giving a string or strings of the names of groups or entities that become attached to and/or detached from the substrate, followed by a suffix that describes the nature of the transformation. Straightforward examples are self-explanatory; for example; 'hydro, chloro-addition'; 'dibromo-elimination'; 'hydroxy-de-iodo-substitution'. For many transformations, particularly substitutions, simplified names are recommended for use in speech or writing (by contrast to the more detailed indexing names). Thus 'hydroxy-de-iodination' may be used instead of 'hydroxy-de-iodo-substitution', or 'nitration' instead of 'nitro-de-hydro-substitution'. A list of non-systematic names is given for transformations that are too complex to be named by the present systematic rules.

Comments should be sent before 30 November 1987 to the Secretary of the Commission on Physical Organic Chemistry, Dr R A Y Jones, School of Chemical Sciences, University of East Anglia, University Plain, Norwich NR4 7TJ, UK.

IUPAC Recommendations on Nomenclature and Symbolism for Mass Spectroscopy

Mass spectroscopy is the study of systems by causing the formation of gaseous ions, with or without fragmentation, which are then characterized by their mass-to-charge ratios and relative abundances. The recommendations contained in this document refer to nomenclature relating to theoretical, technological and experimental aspects of the subject, and to the symbolism used when presenting and discussing mass spectral data.

The Commission on Analytical Nomenclature of IUPAC has previously issued recommendations for nomenclature of mass spectroscopy [*Pure Appl. Chem.*, **37** (1974), pp. 469-480]. These are in the form of definitions of some of the terms used in this subject. In 1978, the Commission on Molecular Structure and Spectroscopy up-dated and extended these recommmendations and, in addition, made further recommendations concerning the use of symbols, acronyms, abbreviations and newly invented jargon [*Pure Appl. Chem.*, **50** (1978), pp. 65-73]. Because the subject continues to expand rapidly, a further compilation of defined terms has become necessary, and the opportunity has been taken to incorporate previous relevant recommendations concerning nomenclature and symbolism in order to produce a single comprehensive document. It is therefore intended that this set of recommendations should replace the earlier publications on the subject.

Comments should be sent before 29 February 1988 to Dr. J F J Todd, University Chemical Laboratory, University of Kent at Canterbury, Kent CT2 7NH, UK.

IUPAC Recommendations on Quantities and Units for Metabolic Processes as a Function of Time

Time-related measurements are peformed in clinical chemistry for a variety of purposes, e.g. in assessing endocrine function by stimulation or suppression tests; to monitor physiological and pathological processes by following the excretion or secretion of components or by measuring catalytic activities of an enzyme in a system. The basis of interpreting and acting upon the test results lies in biochemical, physiological, pharmacological as well as pathological studies. Because of the different origins of such tests, and the varied applications to clinical situations, quantitative results have been presented in a variety of ways in clinical chemistry.

The aims of this document (prepared jointly by

IUPAC Commission on Quantities and Units in Clinical Chemistry and IFCC Expert Panel on Quantities and Units) are: (i) to analyse the elements of the specifications for time-related measurements in the clinical laboratory; and (ii) to recommend a format that will unify, simplify, clarify and hence improve the reporting and understanding of time-related quantities measured in the clinical laboratory.

Comments should be sent before 29 February 1988 to Prof G Férard, Laboratoire de Biochimie Appliquée, Faculté de Pharmacie, Université Louis Pasteur, 74 route du Rhin, BP 10, F-67048 Strasbourg Cédex, France.

Those desirous of having the full texts of these documents may write to the Executive Secretary, Indian National Science Academy, Bahadur Shah Zafar Marg, New Delhi 110 002.

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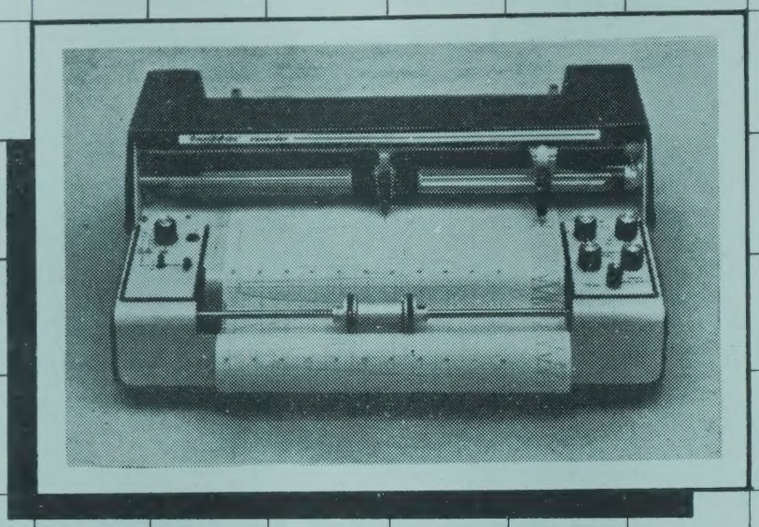

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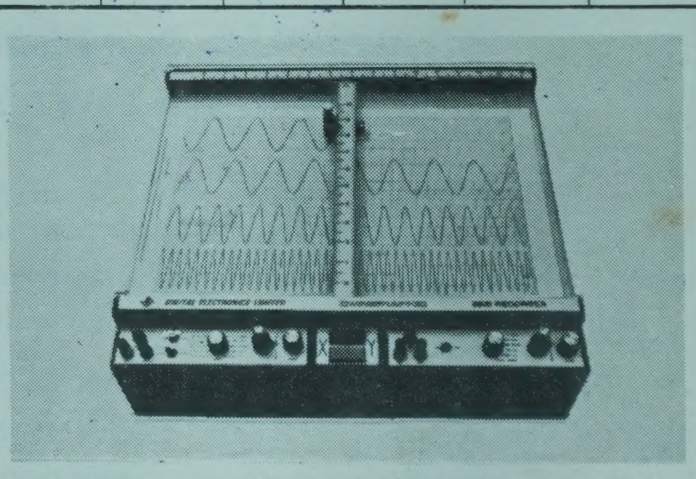

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